

U.S. provisional patent application, which was filed May 11, 2001, and is identified as Attorney Docket No. ORT-1295.

Inventorship of the above-captioned application is disputed at this time. The U.S. provisional application (ORT-1295) was filed only in the names of K. TenHuisen, J. Rosenblatt, and I. Koyfman and the serial number of that provisional patent application has not been provided to inventors A. Cerami, C. Cerami, and Q. Xie. Accordingly benefit is claimed to the parent application using the information available to Applicants A. Cerami, C. Cerami, and Q. Xie.

No new matter has been added.

**CONCLUSION**

Applicants believe that no fee is due for this submission. However, should the Patent Office determine otherwise, please charge the required fee to Pennie & Edmonds LLP Deposit Account No. 16-1150.

Applicants respectfully request entry and consideration of the foregoing amendments and remarks.

Respectfully submitted,

*Laura A. Coruzzi Reg No 30742*

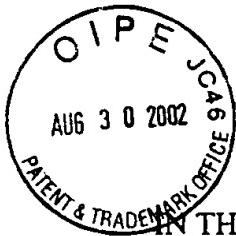
By: *Michael J. Ryan Reg No 41283 30,742*  
Laura A. Coruzzi  
(Reg. No.)

Date: August 20, 2002

**PENNIE & EDMONDS LLP**  
1155 Avenue of the Americas  
New York, NY 10036-2711  
(212) 790-9090

Enclosure

# **EXHIBIT A**



Docket No. 10162-006-999

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : A. Cerami et al.  
Serial No. : 10/017,457  
Filed : December 7, 2001  
Title : IMMUNE MODULATION DEVICE FOR USE IN ANIMALS  
Art Unit : 3736  
Examiner :

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231 on

27 June 2002  
(Date of Deposit)

Hal B. Woodrow  
(Name of applicant, assignee, or Registered Representative)

Hal B. Woodrow  
(Signature)

27 June 2002  
(Date of Signature)

Honorable Commissioner of Patents  
Washington, D.C. 20231

LETTER

1. U. 1648  
Ex'r Lucy

Dear Sir:

I represent Ortho-McNeil Pharmaceuticals, Inc. the assignee of provisional patent application Attorney Docket No. ORT-1295. I investigated the inventorship of the inventions claimed in that provisional patent application and determined that Messieurs TenHuisen, Rosenblatt and Koyfman were the only inventors at the time of filing that application.

The present application (Serial No. 10/103,087) is a copy (with a few minor changes) of provisional patent application Docket No. ORT-1295, that I provided to Ms. Coruzzi of Pennie & Edmonds (who represents Anthony Cerami, Carla Cerami and Qiao-Wen Xie) in confidence. Ms Coruzzi alleged that Anthony Cerami, Carla Cerami and Qiao-Wen Xie were joint inventors. In view of this allegation I had the inventorship of this application investigated again and no facts were found that would support the allegation that Anthony Cerami, Carla Cerami, or Qiao-Wen Xie (Cerami et al.) are joint inventors of the inventions claimed in the provisional patent application or for that matter the present patent application. The Cerami et al's counsel

when repeatedly asked to substantiate the allegation of joint inventorship failed to provide any facts or corroborated evidence to substantiate their claim.

Ms. Coruzzi and Mr. Ryan do not have authority to represent Messieurs TenHuisen, Rosenblatt or Koyfman and Ortho-McNeil Pharmaceuticals, Inc. is under no obligation to assign its rights to the inventions described in the above application to the Ceramis et al.

Ortho-McNeil Pharmaceuticals, Inc. has not granted Cerami et al. the right to claim priority from provisional patent application Docket No. ORT-1295.

Ortho-McNeil Pharmaceuticals, Inc. also has pending a patent application that claims priority from the provisional patent application Docket No. ORT-1295 with similar claims to the present application naming Messieurs TenHuisen, Rosenblatt and Koyfman as the only inventors.

Respectfully submitted,

By: Hal Brent Woodrow  
Hal B. Woodrow  
Reg. No. 32,501

Johnson & Johnson  
One Johnson & Johnson Plaza  
New Brunswick, NJ 08933-7003  
(732) 524-2976  
Dated: June 27, 2002

# PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53 (c).

DOCKET  
NUMBER

ORT-1295

## INVENTOR(s) / APPLICANT(s)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY)
TenHuisen Rosenblatt Koyfman	Kevor Joel Ilya	S. S.	40 Alexandra Way, Clinton NJ 08809 47 Robin Glen Road, Watchung NJ 07060 5 Messenger Lane, Ringoes NJ 08551

## TITLE OF THE INVENTION (280 characters max)

IMMUNE MODULATION DEVICE FOR USE IN ANIMALS

## CORRESPONDENCE ADDRESS

Direct all correspondence to:

Customer Number **000027777**

OR

Firm or Individual Name:

## ENCLOSED APPLICATION PARTS (check all that apply)

<input checked="" type="checkbox"/> Specification	Number of Pages	<input type="checkbox"/> Application Data Sheet  <input type="checkbox"/> CD(s), Number  <input type="checkbox"/> Other (specify) <input style="width: 100px;" type="text"/>
<input checked="" type="checkbox"/> Claims	Number of Claims	
<input checked="" type="checkbox"/> Drawing(s)	Number of Sheets	

## METHOD OF PAYMENT (check one)

<input type="checkbox"/> A check or money order is enclosed to cover the Provisional filing fees.	Provisional Filing Fee Amount (\$)
<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees and credit any overpayment to Deposit Account No. 10-0750	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

No

Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

SIGNATURE: Hal Brent Woodrow

REGISTRATION NO. 35,509

TYPED or PRINTED NAME Hal Brent Woodrow

DATE: May 11, 2001

TELEPHONE (732) 524-2976

## IMMUNE MODULATION DEVICE FOR USE IN ANIMALS

### FIELD OF THE INVENTION

5

The present invention relates to an implantable device and method for modulating the immune response to antigens in mammals. More specifically the present invention provides a porous, implantable device containing a fibrous support and at least one antigen. This device may be used to modulate the immune system to provide a robust response against an antigen, or to down regulate an existing response.

10

### BACKGROUND OF THE INVENTION

Induction of an immune response to an antigen and the magnitude of that response depend upon a complex interplay among the antigen, various types of immune cells, and co-stimulatory molecules including cytokines. The timing and extent of exposure of the immune cells to the antigen and the co-stimulatory milieu further modulate the immune response. Within the body, these various cell types and additional factors are brought into proximity in lymphoid tissue such as lymph nodes.

15

Of the numerous cell types involved in the process, antigen-presenting cells (APC), such as macrophages and dendritic cells, transport antigen from the periphery to local, organized lymphoid tissue, process the antigen and present antigenic peptides to T cells as well as secrete co-stimulatory molecules. Thus, if antigen reaches lymph organs in a localized staggered manner, presenting antigenic epitopes, under the optimal

20

concentration gradient and under the appropriate environment comprising co-stimulatory molecules, a response is induced in the draining lymph node.

25

In this manner, a foreign antigen introduced into the body, such as by means of a vaccination, may or may not result in the development of a desirably robust immune response. Antigens used for vaccination include attenuated and inactivated bacteria and viruses and their components. The success of vaccination depends in part on the type and quantity of the antigen, the location of the site of immunization, and the status of the immune system at the time of vaccination. Not all antigens are equally

immunogenic, and for poorly immunogenic antigens, there are few alternatives available to increase the effectiveness of the immunization. Whereas in experimental animals numerous techniques are available to enhance the development of the immune response, such as conjugating the antigen to a more immunogenic carrier protein or 5 biomolecule (e.g., keyhole limpet hemocyanin), or the use of adjuvants such as Freund's Adjuvant or Ribi. For human vaccinations such techniques and adjuvants are not available. Thus, numerous diseases that would otherwise be preventable by vaccination before exposure to the infectious agent, or in the case of a therapeutic vaccine, that may induce the development of an effective immune response to an 10 existing disease-causing agent or cell, such as cancer, are not available to the patient.

Sponge implant studies have been performed in mammals to assess the immune cell population attracted to a foreign body, which produce what is called a sterile abscess, and sponges prior to or after implantation have been loaded with antigen to 15 further study the attracted cell population. Vallera et al. (1982, Cancer Research 42:397-404) implanted sponges containing tumor cells in mice to examine the composition of cells attracted over a 16 day period, and found that at an early time, cytotoxic cell precursors were present, and cytotoxicity peaked at day 16. Sponges containing tumor cells implanted in mice that had been previously immunized with 20 tumor cells showed a more rapid appearance of cytotoxic cells in the sponge. In neither case did cells from the spleen, lymph nodes or peritoneum show cytotoxicity, which suggested a highly localized response to the antigen in the sponge. Zangemeister-Wittke et al. (1989, J. Immunol. 143:379-385) injected a tumor vaccine into sponges 25 implanted in tumor-immune mice, and monitored the generation of a secondary immune response at the sponge site. No accompanying effect was apparent in lymph nodes adjacent to the implanted sponge.

Other devices which overcome some of the limitations of sponges for 30 immunomodulation have been proposed. US patent 4,919,929 teaches that an antigen can be loaded into solid shaped particles, which slowly release the antigen following implantation. This type of device is envisaged to increase the antibody titers in the milk of mammals and thereby confer higher levels of immunity in those who consume it. WO application 93/17662 describes a device that consists of an impervious

membrane surrounding a core, which is a gel loaded with a therapeutically active ingredient (including antigens). There is at least one port in the impervious membrane that is capable of releasing the active to the surroundings. The use of the membrane is shown to slow the rate of release of the bioactive molecule (including antigens) relative to the gel alone. This device therefore primarily serves as a reservoir for slow release and does not facilitate the interaction of cells with the bioactive, which necessarily must occur outside of the device. In US patent 4,732,155, a device is proposed where there is a reservoir that provides prolonged release of a chemoattractant, which is surrounded by a web of fibers adjacent to the reservoir. Cells are attracted to the reservoir and become trapped in the fibrous web. This device is proposed for use in characterizing allergic and inflammatory responses to test compounds by allowing controlled exposure to the compound and by trapping the cells that respond to it. This device both incorporates a mechanism for prolonged exposure to an antigen as well as a mechanism to facilitate cellular interaction with the antigen. The open web of fibers in this device; however, does not enable local retention of the cytokines and chemokines being secreted by the responding cells since an open web of fibers will not provide diffusional resistance to soluble factors.

This design is improved upon in WO 99/44583 which proposes a porous matrix which is housed in a perforated but otherwise impervious membrane. Antigen is loaded within the device and can be present either as native antigen or can be encapsulated in a slow releasing polymer that provides prolonged presentation of the antigen. Specific cells are attracted to the device by diffusion of the antigen from the perforations in the device and are also able to enter the device through the perforations, but the membrane provides sufficient diffusional resistance that cytokines secreted by cells become locally concentrated within the device. The high local densities of cells and cytokines produce a much more robust immune response than is seen with an uncontained matrix or with simple prolonged release to surrounding tissues.

The preferred embodiment of the device mentioned above envisages the porous matrix to be a sponge and the membrane to be a perforated tube. While very favorable immunomodulation is seen with the device, it is impractical to miniaturize and manufacture in large quantities. The primary reason is that it is very difficult to load a

porous sponge into tubing. Sponges, due to their low bulk densities are mechanically weak and tend to tear easily when subjected to the tensile and compressive forces of loading into small diameter tubing. By reducing the bulk density, more favorable mechanical properties can be encountered however the matrix does not contain  
5 sufficient porosity to attain high cell densities. In addition, it is very difficult to cut small cylindrical cores of porous sponges for loading into tubes. The reason is that the poor mechanical properties of the porous sponge lead to tearing when the size of the piece being cut becomes very small. Consequently, the device envisaged in WO  
99/44583 is only practical to make in diameters of greater than 1 mm. Implantation of  
10 such a large profile device requires a very sizable needle or trochar that would be very painful and cause significant local trauma to a patient. An additional problem with this device design is that it would be difficult to economically manufacture in large quantities. The reason is that each piece of sponge would need to be individually cut and stuffed into the tube. This would be very difficult to mechanize and perform  
15 rapidly.

Accordingly, it would be advantageous to provide an implantable device and method for modulating an immune response to specific antigens in mammals, similar in concept to the design described in WO 99/44583, whose filling preserves the porosity  
20 presented by a porous sponge, which is essential for rapid cellular infiltration, yet overcomes the mechanical frailties of a sponge.

## SUMMARY OF THE INVENTION

25 The present invention is directed to an implantable immune modulation device that is suitable for use in modulating an immune response in mammals, comprising an impermeable shell having a plurality of pores and said impermeable biocompatible shell having an interior lumen, a biocompatible fibrous scaffolding being disposed within said interior lumen. The fibrous scaffolding is loaded with single or multiple  
30 antigens and optionally one or more biologically active compounds such as cytokines (e.g. lymphokines, chemokines etc.), non-cytokine leukocyte chemotactic agents, attachment factors, genes, peptides, proteins, nucleotides, carbohydrates, or cells depending on the application. The shell of the device preferably is made from a

polymer whose glass transition temperature is below physiologic temperature so that the device will minimize irritation when implanted in soft tissues. The shell allows cell ingress but hinders diffusion of soluble molecules out of the device. This helps to concentrate cytokines (e.g. lymphokine and chemokines) secreted by cells which have entered the device in response to loaded antigens and other cells which are present in the device. This local concentration of cells and cytokines significantly enhances the immune response relative to implantation of antigens with standard adjuvants. The fibrous scaffolding provides a scaffold for cells to reside on, process the antigens and interact.

10

Additional benefits of the fibrous scaffolding disclosed in this invention include ease of miniaturization of a device to diameters of less than 1 mm, the possibility of rapid insertion into small diameter tubing or even the ability to have tubing continuously extruded around the matrix.

15

#### **BRIEF DESCRIPTION OF THE FIGURES**

Figure 1 is a perspective drawing of one embodiment of the immune modulating device described herein.

20

Figure 2 is a scanning electron micrograph of one embodiment of a textured fiber suitable for use in the present invention made by the process described in Example 1.

25

Figure 3 is a perspective drawing of one embodiment of the immune modulating device showing one end of the device being sealed.

Figure 4 is a perspective drawing of one embodiment of the immune modulating device showing a device that is crimped.

30

Figure 5 is a perspective drawing of one embodiment of the immune modulating device showing one end of the device being crimped and sealed.

## DETAILED DESCRIPTION OF THE INVENTION

An immune modulation device is disclosed herein which allows for cell ingress and concentration of cytokines secreted by cells. A perspective view of the immune modulation device is provided in Figure 1. The immune modulation device 2 is comprised of a shell 4 surrounding an interior lumen 10. The shell 4 has pores 6 that extend from the outer surface 8 to the interior lumen 10. The interior lumen will have a volume of at least  $1 \times 10^{-8} \text{ cm}^3$ , preferably will be at least  $3 \times 10^{-8} \text{ cm}^3$  and most preferably the size of the lumen will be sufficient to elicit the desired immune response from the animal in which it is implanted (which can be determined by methods well known in the art such as ELISA). The shell 2 may have a variety of three dimensional shapes (e.g. cylindrical, spherical, rectangular, rhomboidal, etc.). For example the shell 2 will generally have a longitudinal axis and a cross-section that may be circular, oval or polygonal. Preferred for ease of manufacture is a cylindrical shape. A cylindrically shaped immune modulation device 2 is illustrated in Figure 1. The ends of the cylindrically shaped immune modulation device may be capped or left open as illustrated in Figure 1. The outer surface 8 of the immune modulation device 2 is preferably impervious to cytokines and immune cells and has numerous pores 6 that allow for the ingress and egress of immune cells. The number of pores 6 will generally be less than 25 percent of the outer surface and preferably will be less than about 10 percent of the outer surface. The pores 6 size may range from about 10 to about 500 microns and preferably in the range of from about 100 to about 400 microns. The interior 10 of immune modulation device 2 will be filled with a fibrous scaffolding 12 made of a plurality of fibers (e.g. a yarn or a tow).

25

The fibrous scaffolding 12 is made from biocompatible fibers, preferably textured fibers which provide a much lower bulk density filling than non-texturized fiber. The low bulk density of textured fibers enables rapid population of the immune modulation device 2 with significant numbers of cells and helps to retain the fibrous scaffolding 12 within the shell 4. The fibrous scaffolding 12 is loaded with single or multiple antigens and optionally other biologically active or pharmaceutically active compounds (e.g. cytokines (e.g. interlukins 1-18; interferons  $\alpha$ ,  $\beta$ , and  $\gamma$ ; growth factors; colony stimulating factors, chemokines, tumor necrosis factor  $\alpha$  and  $\beta$ , etc.), non-cytokine leukocyte chemotactic agents (e.g. C5a, LTB<sub>4</sub>, etc.), attachment factors, genes,

peptides, proteins, nucleotides, carbohydrates or synthetic molecules) or cells depending on the application.

The shell 4 and the fibrous scaffolding 12 of the device will be made with a biocompatible material that may be absorbable or non-absorbable. The device will preferably be made from biocompatible materials that are flexible and thereby minimizing irritation to the patient. Preferably the shell will be made from polymers or polymer blends having glass transition temperature below physiologic temperature. Alternatively the device can be made with a polymer blended with a plasticizer that makes it flexible.

In theory but in no way limiting the scope of this invention it is suspected that the shell allows cell ingress and egress but hinders diffusion of soluble molecules out of the device. This is believed to help to concentrate cytokines secreted by cells that have entered the device in response to loaded antigens (e.g. antigen presenting cells) and other cells (e.g. helper T cells, B cells etc.) which are present in the device. The fibrous scaffolding provides a scaffold for cells to reside on and process the antigens. This local concentration of cells and cytokines significantly enhances the immune response relative to implantation of antigens with standard adjuvants.

The intended recipient of the implantable device is an animal; preferably a human, but also including livestock animal, (e.g. sheep, cow, horse, pig, goat, lama, emu, ostrich or donkey), poultry (e.g. chicken, turkey, goose, duck, or game bird), fish (e.g. salmon or sturgeon), laboratory animal (e.g. rabbit, guinea pig, rat or mouse) companion animal (e.g. dog or cat) or a wild animal in captive or free state.

Numerous biocompatible absorbable and nonabsorbable materials can be used to make the shell or fibrous scaffolding. Suitable nonabsorbable materials for use in as the shell or fibrous scaffolding include, but are not limited to, polyamides (e.g. polyhexamethylene adipamide (nylon 6,6), polyhexamethylene sebacamide (nylon 610), polycapramide (nylon 6), polydodecanamide (nylon 12) and polyhexamethylene isophthalamide (nylon 6I), copolymers and blends thereof), polyesters (e.g. polyethylene terephthalate, polybutyl terephthalate (e.g. as described in EPA 287,899

and EPA 448,840), copolymers (e.g. as described in U.S. Pat. No. 4,314,561; Re 32,770; U.S. Pat. Nos. 4,224,946; 5,102,419 and 5,147,382) and blends thereof), fluoropolymers (e.g. polytetrafluoroethylene and polyvinylidene fluoride copolymers (e.g. as described in U.S. Pat. No. 4,564,013) and blends thereof), polyolefins (e.g. 5 polypropylene including atactic but preferably isotactic and syndiotactic polypropylene and blends thereof, as well as, blends composed predominately of isotactic or syndiotactic polypropylene blended with heterotactic polypropylene and polyethylene), organosiloxanes (e.g. polydimethylsiloxane rubber such as SILASTIC® silicone tubing from Dow Corning), polyvinyl resins (e.g. polystyrene, polyvinylpyrrolidone, etc.) and 10 blends thereof.

Additionally the fibrous scaffolding may be made from natural fibers such as cotton, linen and silk (although silk is referred to as a nonabsorbable material, it is broken down in the human body). Raw silk consists of two filaments that are held 15 together by seracin (silk glue). The silk is degummed (the seracin is removed) and the resulting single filaments are used to manufacture the fiber. The denier per filament (dpf) of individual silk fibers will range from about 0.8 to about 2.0. For fiber manufacture it is common to used silk with a dpf of from about 0.8 to about 1.6 and more preferably a dpf of from about 0.8 to about 1.4. The best grades of silk are easily 20 obtainable from suppliers in China and Japan.

Polyesters are also well known commercially available synthetic polymers that may be used to make the shell or fibrous scaffolding. The most preferred polyester for making this device is polyethylene terephthalate. Generally, polyethylene terephthalate 25 polymers used to make fibers will have a weight average molecular weight of greater than 30,000 preferably greater than 40,000 and most preferably in the range of from about 42,000 to about 45,000. The filaments formed from these polymers should have a tenacity of greater than 5 grams/denier and preferably greater than 7 grams/denier. Polyethylene terephthalate yarns are commonly available from a variety of commercial 30 fiber suppliers (such as E.I. DuPont and Hoechst Celanese). Preferred are commercially available fibers that may be purchased from Hoechst Celanese under the trademark TREVIRA® High Tenacity type 712 and 787 polyester yarns.

A variety of fluoropolymers may also be used to make the shell and the fibrous scaffolding such as polytetrafluoroethylene and polyvinylidene fluoride (i.e. as in U.S. Pat. No. 4,052,550), copolymers and blends thereof. Currently the preferred are the fluoro polymers blends of polyvinylidene fluoride homopolymer and polyvinylidene fluoride and hexafluoropropylene copolymer which is described in U.S. Pat. No. 5 4,564,013 hereby incorporated by reference herein.

As previously stated the term polypropylene for the purposes of this application include atactic but will be preferably isotactic and syndiotactic polypropylene (such as 10 is described in U.S. Pat. No. 5,269,807 hereby incorporated by reference herein) and blends thereof, as well as, blends composed predominantly of isotactic or syndiotactic polypropylene blended with heterotactic polypropylene and polyethylene (such as is described in U.S. Pat. No. 4,557,264 issued Dec. 10, 1985 assigned to Ethicon, Inc. hereby incorporated by reference) and copolymers composed predominantly of 15 propylene and other alpha-olefins such as ethylene (which is described in U.S. Pat. No. 4,520,822 issued Jun. 4, 1985 assigned to Ethicon, hereby incorporated by reference). The preferred polypropylene material for making fibers is isotactic polypropylene without any other polymers blended or monomers copolymerized therein. The preferred method for preparing the flexible polypropylene fibers of the present invention utilizes 20 as the raw material pellets of isotactic polypropylene homopolymer having a weight average molecular weight of from about 260,000 to about 420,000. Polypropylene of the desired grade is commercially available in both powder and pellet form.

A variety of bioabsorbable polymers can be used to make the shell or fibrous 25 scaffolding of the present invention. Examples of suitable biocompatible, bioabsorbable polymers include but are not limited to polymers selected from the group consisting of aliphatic polyesters, poly(amino acids), copoly(ether-esters), polyalkylenes oxalates, polyamides, tyrosine derived polycarbonates, poly(iminocarbonates), polyorthoesters, polyoxaesters, polyamidoesters, polyoxaesters 30 containing amine groups, poly(anhydrides), polyphosphazenes, biomolecules (i.e., biopolymers such as collagen, elastin, bioabsorbable starches, etc.) and blends thereof.

For the purpose of this invention aliphatic polyesters include, but are not limited to, homopolymers and copolymers of lactide (which includes lactic acid, D-, L- and meso lactide), glycolide (including glycolic acid),  $\epsilon$ -caprolactone, p-dioxanone (1,4-dioxan-2-one), trimethylene carbonate (1,3-dioxan-2-one), alkyl derivatives of trimethylene carbonate, delta-valerolactone, beta-butyrolactone, gamma-butyrolactone,  $\epsilon$ -decalactone, hydroxybutyrate, hydroxyvalerate, 1,4-dioxepan-2-one (including its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione), 1,5-dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one, 2,5-diketomorpholine, pivalolactone, gamma, gamma-diethylpropiolactone, ethylene carbonate, ethylene oxalate, 3-methyl-1,4-dioxane-2,5-dione, 3,3-diethyl-1,4-dioxan-2,5-dione, 6,8-dioxabicyclooctane-7-one and polymer blends thereof. Poly(iminocarbonates), for the purpose of this invention, are understood to include those polymers as described by Kemnitzer and Kohn, in the Handbook of Biodegradable Polymers, edited by Domb, et. al., Hardwood Academic Press, pp. 251-272 (1997). Copoly(ether-esters), for the purpose of this invention, are understood to include those copolyester-ethers as described in the Journal of Biomaterials Research, Vol. 22, pages 993-1009, 1988 by Cohn and Younes, and in Polymer Preprints (ACS Division of Polymer Chemistry), Vol. 30(1), page 498, 1989 by Cohn (e.g. PEO/PLA). Polyalkylene oxalates, for the purpose of this invention, include those described in U.S. Patent Numbers 4,208,511; 4,141,087; 4,130,639; 4,140,678; 4,105,034; and 4,205,399 hereby incorporated by reference herein.

Polyphosphazenes, co-, ter- and higher order mixed monomer-based polymers made from L-lactide, D, L-lactide, lactic acid, glycolide, glycolic acid, para-dioxanone, trimethylene carbonate and epsilon-caprolactone such as are described by Allcock in The Encyclopedia of Polymer Science, Vol. 13, pages 31-41, Wiley Intersciences, John Wiley & Sons, 1988 and by Vandorpe, et al in the Handbook of Biodegradable Polymers, edited by Domb, et al, Hardwood Academic Press, pp. 161-182 (1997).

Polyanhydrides include those derived from diacids of the form HOOC-C<sub>6</sub>H<sub>4</sub>-O-(CH<sub>2</sub>)<sub>m</sub>-O-C<sub>6</sub>H<sub>4</sub>-COOH, where m is an integer in the range of from 2 to 8, and

- copolymers thereof with aliphatic alpha-omega diacids of up to 12 carbons.
- Polyoxaesters, polyoxaamides and polyoxaesters containing amines and/or amido groups are described in one or more of the following U.S. Patent Nos. 5,464,929; 5,595,751; 5,597,579; 5,607,687; 5,618,552; 5,620,698; 5,645,850; 5,648,088; 5,698,213; 5,700,583; and 5,859,150 hereby incorporated herein by reference.
- 5 Polyorthoesters such as those described by Heller in Handbook of Biodegradable Polymers, edited by Domb, et al, Hardwood Academic Press, pp. 99-118 (1997).
- As used herein, the term "glycolide" is understood to include polyglycolic acid.
- 10 Further, the term "lactide" is understood to include L-lactide, D-lactide, blends thereof, and lactic acid polymers and copolymers.
- Particularly well suited for use in the present invention are biocompatible absorbable polymers selected from the group consisting of aliphatic polyesters, 15 copolymers and blends which include but are not limited to homopolymers and copolymers of lactide (which includes D-, L-, lactic acid and D-, L- and meso lactide), glycolide (including glycolic acid), epsilon-caprolactone, p-dioxanone (1,4-dioxan-2-one which is described in U.S. Pat. No. 4,052,988 incorporated herein by reference herein), alkyl substituted derivatives of p-dioxanone (i.e. 6,6-dimethyl-1,4-dioxan-2- 20 one which is described in U.S. Pat. No. 5,703,200 assigned to Ethicon and hereby incorporated by reference), trimethylene carbonate (1,3-dioxan-2-one), alkyl substituted derivatives of 1,3-dioxanone (which are described in U.S. Pat. No. 5,412,068 incorporated herein by reference), delta-valerolactone, beta-butyrolactone, gamma-butyrolactone, epsilon-decalactone, hydroxybutyrate, hydroxyvalerate, 1,4-dioxepan-2- 25 one (described in U.S. Pat. No. 4,052,988 and its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione which is described in U.S. Pat. No. 5,442,032 assigned to Ethicon and hereby incorporated herein by reference), 1,5-dioxepan-2-one, and polymer blends thereof. Preferred fiber materials include but are not limited to copolymers of trimethylene carbonate, epsilon-caprolactone and glycolide (such as are 30 described in U.S. Pat. Nos. 5,431,679 and 5,854,383 hereby incorporated by reference) and copolymers of p-dioxanone, trimethylene carbonate and glycolide and

copolymers of lactide and p-dioxanone. Preferred are fibers made from lactide and glycolide sometimes referred to herein as simply homopolymers and copolymers of lactide and glycolide and copolymers of glycolide and epsilon-caprolactone i.e. as described in U.S. Pat. Nos. 5,133,739; 4,700,704 and 4,605,730 incorporated herein by reference), most preferred for use as a fiber is a copolymer that is from about 80 weight percent to about 100 weight percent glycolide with the remainder being lactide. More preferred are copolymers of from about 85 to about 95 weight percent glycolide with the remainder being lactide.

The molecular weight of the polymers used in the present invention can be varied as is well known in the art to provide the desired performance characteristics. However, it is preferred to have aliphatic polyesters having a molecular weight that provides an inherent viscosity between about 0.5 to about 5.0 deciliters per gram (dl/g) as measured in a 0.1 g/dl solution of hexafluoroisopropanol at 25 °C, and preferably between about 0.7 and 3.5 deciliters per gram (dl/g).

As mentioned above, the outer surface 8 of shell 4 will be perforated with pores 6, which provide a passageway for the ingress and egress of cells to the interior lumen 10 of the immune modulation device 2. At the time of implantation the shell 2, is substantially impermeable to diffusion of water through the non-perforated walls of the shell. The shell 2 is preferably made from one or more absorbable polymers that may become more permeable to aqueous media as they degrade. Absorbable polymers can either be of natural or synthetic origin. The absorbable polymers for the membrane most preferably have a glass transition temperature below physiologic temperature and would therefore be less irritating when implanted in soft tissues. Preferred polymers for the shell would include copolymers with a significant content (at least 30 weight percent) of epsilon-caprolactone or para-dioxanone. A particularly desirable composition includes an elastomeric copolymer of from about 35 to about 45 weight percent epsilon-caprolactone and from about 55 to about 65 weight percent glycolide, 30 lactide (or lactic acid) and mixtures thereof. Another particularly desirable composition includes para-dioxanone homopolymer or copolymers containing from about 0 to about 80 weight percent para-dioxanone and from about 0 to about 20 weight percent of either lactide, glycolide and combinations thereof. The degradation time for the membrane

in-vivo is preferably longer than 1 month but is shorter than 6 months and more preferably is longer than 1 month but less than 4 months.

The shell 4 can be of any shape into which the fibrous scaffolding can be placed. The shell can initially have openings that may be later sealed following placement of the fibrous scaffolding 12. The shell 4 can be made by conventional polymer processing techniques including molding, welding, casting, extrusion, injection molding, machining process or combinations thereof. These conventional procedures are well known in the art and described in the Encyclopedia of Polymer Science and Engineering, incorporated herein as reference. Melt extrusion is the preferred method of process as it is rapid, inexpensive, scalable, and can be performed solvent-free for many polymers of interest. Processing aides and plasticizers can be added to the polymer to decrease the processing temperature and/or modify the physical properties of the construct. Processing aides, such as solvents, can be added to decrease the processing temperature by decreasing the glass transition temperature of the polymer. Subsequently, the aide can be removed by either heat and/or vacuum or by passing the extruded construct through a secondary solvent in which the polymer has minimal solubility but is miscible with the processing aide. For example halogenated solvents such as methylene chloride or chloroform can be added to homo- and copolymers of lactide and epsilon-caprolactone. After extrusion, the solvent can be removed through evaporation, vacuum, and/or heat. These solvents could also be extracted by passing the extrudate through a secondary solvent such as alcohol, which has miscibility with the halogenated solvent. Plasticizers can also be incorporated into a polymer to increase its workability, flexibility, or distensibility. Typically these materials work by increasing the free volume of the polymer. For example many citrates, malates and caprilates will work to plasticize many aliphatic polyesters. Oligomers of a given polymer or copolymer can also be used to plasticize a system.

The preferred shapes of the shell are those with a minimal diameter in one dimension to facilitate placement using a small gauge needle. A most preferred shape is a cylinder with an outer diameter preferably less than 1 millimeter and most preferably less than 750 microns. This shape and size facilitates implantation of the device using an 18 gauge needle or smaller. For this embodiment it is preferred that the

wall thickness is preferably less than 250 microns and most preferably is less than 150 microns. The pores 6 in the shell 4 generally are large enough to provide for the ingress and egress of cells. The pores are preferably larger than about 10 microns but smaller than about 500 microns in cross-sectional diameter and more preferably are from about 5 100 to about 400 microns in cross-sectional diameter. The density of perforations preferably does not exceed 25% of the outer surface area of the device and more preferably is below 10% of the outer surface area of the shell of the immune modulation device. The pores can be formed using any appropriate drilling technique (e.g. using a hypodermic needle, mechanical or laser) or alternatively by including a 10 solvent or water soluble solid in the wall polymer which later can be leached out by immersing the tube in the solvent to generate the hole. Alternatively, if biocompatible water soluble particles such as sugars, amino acids, polymers such as PVP, proteins such as gelatin, carbohydrates such as hyaluronic acid and certain carboxy methylcelluloses are used, the device can be implanted with the particles present. Upon 15 exposure to body fluids the pore forming particles can leach out or degrade forming pores. Most of the pore must extend completely through the wall of the device and provide a pathway for cells involved in the immune response to ingress into the interior lumen 10 of the device as well as for antigen and cytokines to diffuse out of the interior lumen 10 of the immune modulation device 2. If the immune modulation device 2 has 20 one or more open ends 14 of the immune modulation device can either be sealed with layer 16 or left open, but are preferably left open. One embodiment of an immune modulation device with one sealed end is illustrated in Figure 3.

In another embodiment of the present invention two portions of the interior 25 surface 18 may contact the fibrous scaffolding 12 to restrain movement of the fibers in the immune modulation device 2. For example if the immune modulation device 2 were cylindrical a portion of the device could be crimped about the fibrous scaffolding 12. The crimping could be performed with heating to permanently reshape a portion of the shell 4. One embodiment of a crimped device is illustrated in Figure 4. 30 Alternatively, the crimping could be performed with cutting and sealing one end of the immune modulation device 2 to form a cylindrical device with one sealed end 20. One embodiment of this device with a sealed end is illustrated in Figure 5.

Fibers suitable for use in the present device can be made using conventional spinning processes such as melt spinning processes or solution spinning. After spinning the yarns may be quenched, treated with a spin finish, drawn and annealed as is known in the art. The fibrous scaffolding made from these fibers should have a porosity of greater than 20%, more preferably from about 25% to about 95%, and most preferably from about 30% to about 90% to the fibers.

The fibrous scaffold should be made up of filaments having a denier in the range of from about 0.2 to about 10 and preferably a denier from about 0.8 to about 6 and more preferably a denier of from about 1 to about 3. The filaments are commonly extruded in bundles (yarns) having a denier in the range of from about 20 to about 400 denier and preferably about 50 to about 100 denier. The fibers need to be treated to develop the bulk density or porosity need for a fibrous scaffold. The preferred yarns for this application are textured yarns. There are many forms of textured yarns that may be used to form a fibrous scaffolding such as bulked yarns, coil yarns, core bulked yarns, crinkle yarns, entangled yarns, modified stretch yarns, nontorqued yarns, set yarns, stretch yarns and torqued yarns and combinations thereof. Methods for making these yarns are well known and include the false-twisted method, entanglement (e.g. rotoset or air jet entangled), crimping (e.g. gear crimped, edge crimped or stuffer box crimped), and knit-de-knit. Preferably the fibers will be textured by false-twisting method, the stuffer box method or knit-de-knit method of textile texturing. The filaments are texturized to provide a high degree of permanent crimping or random looping or coiling. Crimped fibers are currently preferred. Crimping causes the orientation of the filament to change angle at the crimping points. The angle change is preferably greater than 10 degrees at each crimp point. The crimping can be accomplished through a variety of processes but is most easily generated by feeding the extruded filaments through a stuffer box.

The fibrous scaffolding is preferably a texturized fiber made from an absorbable polymer that can either be of natural or synthetic origin. Each fiber filament preferably has a diameter of less than 20 microns and most preferably less than 15 microns. This imparts to the filaments sufficient flexibility to completely fill the lumen of the tube and provide a suitable surface for cells to colonize in the lumen of the shell. The fibers

preferably will take longer than 1 month to biodegrade (via hydrolysis and/or enzymatic activity) in a normal subcutaneous implantation but will completely be biodegraded within 6 months and more preferably between 1 and 4 months. An example of a good polymer for making a fibrous scaffolding is a copolymer of 90% glycolide (or glycolic acid) and 10% lactide (or lactic acid) having an inherent viscosity between about 0.7 to about 1.5 deciliters per gram (dl/g) as measured in a 0.1 g/dl solution of hexafluoroisopropanol at 25°C.

The most significant advantage with the use of fibrous scaffolding is that the fibers can be easily placed within the shell. For example, a textured fiber can be stretched and then the shell extruded, molded or otherwise coated or shaped around them. Following placement of the shell around the stretched fibers, the tension can be relaxed which allows the fibers to assume their crimped shapes and fill the space inside the shell. Unlike sponges that can also be compressed, the textured fibers can be wound onto spools in very long lengths, which can be continuously fed as a core in a core-sheath or wire coating extrusion process. The sheath can be a molten polymer that is co-extruded and drawn with the stretched fibers. Individual units could be created by cutting the core sheath constructs to a desired length. Perforations can be created by piercing the tubing wall to form small holes. Open pore sponges are very difficult to produce in a continuous form and hence would require the shell be formed as small discrete units into which the sponge can be stuffed.

An additional advantage of fibrous scaffolding over sponges in processing is that the spool of fibers will be strong while an open cell sponge will be weak and will tear easily. This is an important consideration in miniaturization of the device. Small bunches of fibers can be stretched, compressed or otherwise exposed to robust mechanical processing. In contrast, small dimension sponges tear or break easily and can only be subjected to gentle processing. Formation of sub-millimeter devices necessarily subjects the filling to significant stresses in order to fit within the small dimensions of the shell. Miniaturization is very important in minimizing patient pain and discomfort following implantation of the device. Hence the use of fibers, which can be compressed more substantially than an open-cell sponge, enables a smaller device which is preferable from the patient's standpoint.

At first glance it may appear desirable to fill the shell with simple straight fibers. However, straight fibers would settle and bunch in the shell over time and would not provide a hospitable environment for ingress of large numbers of cells.

- 5     Additionally, straight fiber would require that the device be modified to prevent the fibers from fall out of the device during handling. If the fibers were densely packed or braided so as to provide an interference fit in the shell there would not be sufficient porosity for cell colonization. Texturizing the fibers allows them to effectively fill space while maintaining porosities needed for colonization with high cell number
- 10    densities. This low bulk density property of the texturized fibers enables an interference fit with the walls of the shell without having to worry about compaction of the filling during storage and handling.

15    The textured fibers can either be filled into a preformed tube or the tube can be extruded around the filaments. During the filling process it may be desirable to stretch the filaments to a straight orientation. This radially compresses the fibers to a much smaller diameter than they occupy when in a relaxed state. The void volume in the lumen of the tube is preferably greater than 30% and more preferably greater than 50%. Once relaxed the textured filaments should completely fill the lumen of the device and

20    should stay in place in the lumen due to the compressive force exerted by the tubing walls on the filling.

A preferred process for generating the textured fiber filled tubes consists of extruding the tubing around the stretched filaments in a continuous manner. This can be accomplished by having the textured fiber wound on a spool and fed under tension through the lumen of an extruder die as a core around which a sheath of wall polymer is continuously extruded. Perforations can later be drilled through the wall of the polymer either mechanically or using electromagnetic radiation (e.g. laser ablation). It is especially desirable to adjust the depth of drilling so that the wall is completely punctured but the filling is not damaged. With electromagnetic radiation this can be accomplished by provided just enough focused energy to ablate through the wall of the tube. Alternatively it is possible to fill a preformed tube by tying the textured fiber to a thin wire or needle and then dragging the textured filaments under tension through the

tubing. Additionally, it is possible to fill a preformed tube by using a pressure differential (e.g. vacuum or blown air) to pull the textured filament through the tubing. In this configuration the perforations in the tube can be created either pre or post filling of the lumen. The length of the textured fiber filled tube is cut to be greater than a few millimeters and more preferably greater than 5 millimeters.

The lumen of the device is filled with an antigen, mixture of antigens and optionally one or more cytokines, prior to implantation. The antigen can either be in a dry or wet form. Potential antigens include peptides, proteins, nucleotides, carbohydrates or even cells or cell fragments. The antigen or antigens can be bioavailable at the time of implantation (for immediate release with optionally a portion in a sustained release form) or designed to be bioavailable after implantation (e.g. 3 days after). The antigen or antigens can be supplied in a sustained release form, such as encapsulated in microparticles, can be supplied in a naked form or in combinations thereof. One method by which antigen can be loaded is to suspend it in a suitable liquid which is then injected or pumped into the lumen of the filled tube. The textured fiber filling must be under sufficient compression as to stay in place through the convection of the fluid. The fluid filled device can then be implanted or the filling fluid can be dehydrated or lyophilized prior to implantation leaving behind in the lumen of the filled device the desired antigen or antigens. Alternatively the textured fiber may be impregnated with the antigen etc. prior to insertion into the shell. The dehydrated system will rehydrate following implantation that will present the antigen in a suitable form for generating the desired immunomodulatory response. A particularly convenient site of implantation is subcutaneous insertion directly beneath the skin, however any site which offers access to antigen presenting cells, macrophages and other cells of the immune system is acceptable. Desired immunomodulatory responses can include either generation of humoral and/or cellular immunity against the desired antigen or alternatively desensitization towards particular allergen or cell types.

Any specific antigen or combination of synthetic or natural antigens may be employed as the antigenic substance for incorporation in the immune modulation device and subsequent implantation in the animal. The antigens can be bacterial, fungal, viral, cellular (e.g. from parasites or in autoimmune treatments from animal

tissue) or synthetic epitope to which the immune system of the animal will respond. Preferably for mammals, the antigen or mixtures of antigens are bacterial or viral with polyvalent antigens also being preferred. Suitable bacterial antigen sources include *Actinobacillus equuli*, *Actinobacillus lignieresii*, *Actinobacillus seminis*, *Aerobacter aerogenes*, *Borrelia burgdorferi*, *Babesia microti*, *Klebsiella pneumoniae*, *Bacillus cereus*, *Bordetella pertussis*, *Brucella abortus*, *Brucella melitensis*, *Brucella ovis*, *Brucella suis*, *Brucella canis*, *Campylobacter fetus*, *Campylobacter fetus intestinalis*, *Chlamydia psittaci*, *Chlamydia trachomatis*, *Clostridium tetani*, *Corynebacterium acne* Types 1 and 2, *Corynebacterium diphtheriae*, *Corynebacterium equi*, *Corynebacterium pyogenes*, *Corynebacterium renale*, *Coxiella burnetii*, *Diplococcus pneumoniae*, *Escherichia coli*, *Ehrlichia phagocytophila*, *Ehrlichia equi*, *Fusobacterium necrophorum*, *Granuloma inguinale*, *Haemophilus influenzae*, *Haemophilus vaginalis*, Group b *Hemophilus ducreyi*, *Lymphopathia venereum*, *Leptospira pomona*, *Listeria monocytogenes*, *Microplasma hominis*, *Moraxella bovis*, *Mycobacterium tuberculosis*, *Mycobacterium laprae*, *Mycoplasma bovigenitalium*, *Neisseria gonorrhoea*, *Neisseria meningitidis*, *Pseudomonas maltophilia*, *Pasteurella multocida*, *Pasteurella haemolytica*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Rickettsia prowazekii*, *Rickettsia mooseri*, *Rickettsia rickettsii*, *Rickettsia tsutsugamushi*, *Rickettsia akari*, *Salmonella abortus ovis*, *Salmonella abortus equi*, *Salmonella dublin*, *Salmonella enteritidis*, *Salmonella heidelberg*, *Salmonella paratyphi*, *Salmonella typhimurium*, *Shigella dysenteriae*, *Staphylococcus aureus*, *Streptococcus ecoli*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Streptococcus mutans*, *Streptococcus* Group B, *Streptococcus bovis*, *Streptococcus dysgalactiae*, *Streptococcus equisimili*, *Streptococcus uberis*, *Streptococcus viridans*, *Treponema pallidum*, *Vibrio cholerae*, *Yersina pesti*, *Yersinia enterocolitica* and combinations thereof. Suitable fungi antigen sources include *Aspergillus fumigatus*, *Blastomyces dermatitidis*, *Candida albicans*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum* and combinations thereof. Suitable viral antigen sources include influenza, HIV, human papilloma virus, cytomegalovirus, polio virus, rabies virus, Equine herpes virus, Equine arteritis virus, IBR--IBP virus, BVD--MD virus, Herpes virus (humonis types 1 and 2) and combinations thereof. Suitable parasite antigen sources include but are not limited to *Schistosoma*, *Plasmodium*, *Onchocerca*, parasitic amoebas and combinations thereof. Preferred infectious diseases that this device and method may provide prophylaxis

against include viruses such as influenza, HIV, Papilloma, hepatitis, cytomegalovirus, polio and rabies; bacteria for example *E. coli*, *Pseudomonas*, *Shigella*, *Treponema pallidum*, *Mycobacterium* (*tuberculosis* and *laprae*), *Chlamydia*, *Rickettsiae*, and *Neisseria*; fungi such as *Aspergillus* and *Candida*; and parasitic, protozoan 5 multicellular pathogens such as *Schistoma*, *Plasmodium* and amoebae.

Suppression of the immune response may also be desirable to treat conditions, such as allergies, or to prepare patients for the exposure to foreign antigens, such as for transplant. Inappropriate immune responses are believed to be the underlying etiology 10 in a number of autoimmune and other diseases, such as type I diabetes, rheumatoid arthritis, multiple sclerosis, uveitis, systemic lupus erythematosus, myasthenia gravis, and Graves' disease. By implanting in an individual a device of the present invention containing the suspect antigen, entry of cells primed to recognize the antigen can be induced to undergo apoptosis, and be eliminated from the immune system. Elimination 15 of progenitor antigen-specific cells can permit the later transplant of foreign antigens without rejection.

Further utilities of the present invention include improvements in the generation 20 of polyclonal antibodies (immune serum) and nonclonal antibodies in laboratory animals and obtaining the desired isotype of antibody so generated. In one embodiment, a procedure for preparing polyclonal (immune serum) and monoclonal antibodies against an antigen available only in minute quantities can be performed by the device of the present invention. The device can be provided with a small amount of 25 the rare antigen, in order to immunize the animal, after which spleen cells can be harvested. This procedure offers an improvement over current tedious and unpredictable method of introducing the rare antigen directly into the spleen. Furthermore, the need for a boost immunization may be obviated by use of the device 30 of the present invention, and, in addition, an immune response will be generated more quickly. A shortened time required to immunize animals will allow the generation of monoclonal antibodies more rapidly. In another embodiment, immune cells for the production of hybridomas can be harvested from the device after immunization of an animal with an antigen provided within the device. This procedure can also be used to generate human monoclonal antibodies, by implanting a device of the present invention

into an individual, loading the device with antigen, and then harvesting immune cells from the device for the production of hybridomas. The above-mentioned polyclonal antibodies (immune serum) and monoclonal antibodies can be used for diagnosis, basic research, imaging and/or therapy. In another embodiment, human monoclonal antibodies can be generated using the device of the present invention implanted in a severe combined immunodeficiency (SCID) mouse, by the following procedure. First, 5 human peripheral blood lymphocytes are injected into a SCID mouse, wherein the human lymphocytes populate the murine immune system. After implantation of a device of the present invention comprising the desired antigen which is bioavailable after implantation, subsequent harvesting of cells from the device will provide human B 10 lymphocytes cells which can then be used to prepare hybridomas which secrete human antibodies against the desired antigen.

A further utility of the device of the present invention is in collection of immune 15 cells from a mammal for later reintroduction into the mammal. Cells can be removed from the device, for example, by aspiration from the implanted device or collection from the device after removal from the body by dissolving the polymer matrix, subsequent storage of the cells, for example by cryopreservation, and reintroduction into the mammal at a later time. This can be particularly useful for mammals undergoing whole body radiation therapy. A device of the present invention, without 20 containing antigen, can be implanted and maintained for a time sufficient to allow immune cells to migrate into the device (e.g. seven to ten days). Subsequently the device or its contents are removed and the cells contained therein cryopreserved. Following radiation therapy, the mammal can have the cells reintroduced into the body, 25 whereby the cells will reconstitute the immune system. In another embodiment of this utility, co-stimulatory factors such as cytokines which induce the proliferation of immune cells can be introduced into the device to increase the yield of cells within the device, before harvesting. In a further embodiment, immune cells collected from a device provided with antigen can be used for active immunization, wherein the cells 30 can be stored and then reintroduced into the mammal after, for example, a course of chemotherapy or other therapeutic manipulation. In a still further embodiment, cells collected from a device can be cryopreserved, and at a later time be exposed to the

antigen (for example, a cancer antigen) for ex-vivo propagation of T cells prior to introduction into the body, for adoptive immunotherapy.

## EXAMPLES

5

The following examples illustrate the construction of a textured fiber filled device for generating an immunomodulatory response. Those skilled in the art will realize that these specific examples do not limit the scope of this invention and many alternative forms of an antigen loaded textured fiber filled device could also be generated within the scope of this invention.

10

### EXAMPLE 1

#### TEXTURED FIBROUS FILLING

15 Fiber texturing was performed using a Techtex® HDC10 texturizer (Techniservice, 738 West Cypress Street, Kennett Square, PA 19348-0817). Nine spools of 56 denier natural 90/10 glycolide-co-lactide (IV of about 1.1 deciliters per gram (dl/g) as measured in a 0.1 g/dl solution of hexafluoroisopropanol at 25 °C. The filaments had been drawn about 5X (original length compared to final length). The 20 filaments were placed on the creel and combined into a single 504 denier tow by running the drawn yarns together through a common eyelet. The individual yarn filament diameters were between 12-20 µm. A pretension of 5-7 grams was used for each yarn by passing them through the gate tensioner. The large yarn tow was then passed over a heated godet with the separator roller (15 wraps) with the heated godet 25 being set to a temperature of 130°C. This yarn tow was then fed into the stuffer box by two crimpler rolls. The clearance between the stuffer box and rollers was 0.012 inches and the temperature in the stuffer box was about 50°C (the box was not heated, the elevated temperature of 50°C came from the yarn, heated on the godet). Uniformity of 30 crimp texture is maintained through accurate control of the crimped column height in the stuffer box. The column height control is provided by the optical sensor located in the stuffer box and signaling the take up winder inverter to speed up/slow down. The stuffer box optical sensor was set to hole no. 8 from the top of the box. After the stuffer box, the textured yarn tow passed through the gate tensioner set at 5 grams for

combining and keeping all yarns in the tow under the same tension. The crimped yarn then passed the overfeed rolls to reduce high yarn tension prior to winding on the take up winder. The take up winder speed was set at 170 m/min. An image of the resulting textured fiber is shown in Figure 2.

## 5 EXAMPLE 2

### MEMBRANE FORMATION

Membranes were formed from both poly(para-dioxanone) (PDO) and a copolymer of 35/65 epsilon-caprolactone/glycolide (CAP/GLY). The inherent viscosity (dl/g) of the PDO and CAP/GLY, as measured in a 0.1g/dl solution of hexafluoroisopropanol (HFIP) 25°C, were 1.80 and 1.30, respectively. All membranes were formed by extrusion using a 3/4-inch Brabender single-screw extruder (C.W. Brabender® Instruments, Inc., So. Hackensack, NJ) under flowing nitrogen. Membranes with several inner and outer dimensions were formed. Extrusion conditions for the extruded membranes are shown in Table 1. Immediately following exit from the die, all membranes were run through a 12-foot cooling trough filled with chilled water at a temperature of 5-10°C. For the CAP/GLY membranes, short segments (~2-3 ft.) were cut and hung from one end at room temperature to allow solidification and crystallization of the polymer.

20 Table 1: Extrusion conditions

Polymer	Die size Die x tip (mil)	T <sub>zone1</sub> (°C)	T <sub>zone2</sub> (°C)	T <sub>zone3</sub> (°C)	T <sub>adapt.</sub> (°C)	T <sub>die</sub> (°C)	P <sub>block</sub> (psi)	P <sub>air</sub> (psi)	Screw speed (rpm)	Take- off (FTM)	OD (mm)	ID (mm)
35/65 CAP/GLY	170 x 138	140	145	145	145	140	1900	0.1	12	20	2.0	1.5
35/65 CAP/GLY	102 x 83	140	145	145	145	145	4480	0	4	18	1.03	0.83
35/65 CAP/GLY	53 x 40	140	145	145	145	140	4300	0.1	3	14	0.9	0.7
35/65 CAP/GLY	56 X 40	140	145	150	150	150	2470	0.3	4	34	0.65	0.45
PDO	102 X 83	130	135	135	135	135	5000	0	5	20	1.03	0.83
PDO	102 X 83	145	150	150	150	150	3750	0	5	20	0.65	0.45

After extrusion, the membranes were cut to the desired length (2-2.5 cm) using a razor blade. Membrane perforations were formed at Resonetics, Inc. (Nashua, NH) using an excimer laser (Lambda-Physik EMG201MSC Excimer Laser) operating at a wavelength of 193 nm. The laser was coupled to a Resonetics engineering workstation

consisting of a mask projection imaging beam delivery system and a three-axis (XYtheta) computerized motion control system. Hole sizes ranging between 100 and 500 microns were formed through the membrane walls. Drilling parameters for the different tubing are shown in Table 2.

5

Table 2: Laser drilling conditions

Polymer	OD/ID (mm/mm)	Fluence (J/cm <sup>2</sup> )	Pulse rate (Hz)	~ Etch rate ( $\mu\text{m}/\text{pulse}$ )
35/65 CAP/GLY	2.0x1.5, 0.9x0.7	10	50	0.63
35/65 CAP/GLY	2.0x1.5	3.5	50	0.56
35/65 CAP/GLY	2.0x1.5	0.7	10	0.5
35/65 CAP/GLY	1.03x0.83, 0.65x0.45	2	25	0.67
PDO	1.03x0.83, 0.65x0.45	2.6	50	0.5

10    **EXAMPLE 3**

VLN CONSTRUCT FORMATION

The textured fiber filling from Example 1 was placed inside the membranes discussed in Example 2 as follows. Textured fiber was attached to a small needle or thin filament of wire and pulled through the membrane. The fiber was cut to the length 15 of the membrane. Available porosity was calculated from the volume of the inner lumen of the membrane, weight of textured yarn placed inside of the membrane, and the density of the fibers used. Table 3 shows several of the construct geometries and resultant porosities.

**Table 3:** Absorbable VLN constructs containing textured fiber.

Membrane Composition	OD/ID/length (mm/mm/mm)	Hole diameter ( $\mu\text{m}$ )	# holes	Fiber weight (mg)	~ Percent porosity	Sample #
CAP/GLY	2.0/1.5/25	300	20	12	80%	1
CAP/GLY	2.0/1.5/20	300	16	10	80%	2
CAP/GLY	2.0/1.5/20	300	12	10	80%	3
CAP/GLY	2.0/1.5/20	300	8	10	80%	4
CAP/GLY	2.0/1.5/20	300	4	10	80%	5
CAP/GLY	2.0/1.5/20	not applicable	0	10	80%	6
CAP/GLY	2.0/1.5/25	300	16	10	83%	7
CAP/GLY	2.0/1.5/25	300	16	15	75%	8
CAP/GLY	2.0/1.5/20	300	20	8	83%	9
CAP/GLY	2.0/1.5/20	300	20	12	75%	10
CAP/GLY	0.65/0.45/25	150	4	2	65%	11
CAP/GLY	0.65/0.45/25	150	12	2	65%	12
CAP/GLY	0.65/0.45/25	150	20	2	65%	13
PDO	0.65/0.45/25	150	4	1.3	75%	14
PDO	0.65/0.45/25	150	8	1.3	75%	15
PDO	0.65/0.45/25	150	12	1.1	80%	16
PDO	0.65/0.45/25	150	16	1.3	75%	17

5

#### EXAMPLE 4

Prior art (WO 99/44583) has demonstrated that a nonabsorbable device using a 25 mm length of silicone tubing with an internal diameter of 1.5 mm and outer diameter of 2 mm, fitted with a 25 mm-long segment of hydroxylated polyvinyl acetate sponge induces a more robust immune response to the influenza vaccine (in BALB/c mice) than traditional intramuscular injections with and without the use of traditional adjuvants such as Ribi. Similarly the device of the present invention such as the absorbable, fiber-filled device described in Example 3 (Sample #1) could be loaded with ~100 ng of influenza antigen (FLUSHIELD® influenza virus vaccine, trivalent, Types A & B; obtained from Henry Schein®, Melville NY). Female BALB/c mice (6-8 weeks old) would be anesthetized with Avertin. One device per animal could be inserted through a 0.5-cm dorsal midline incision on day 1.

At appropriate intervals post-immunization the mice could be bled and the sera tested for influenza-specific humoral response, using conventional ELISA or other appropriate protocols to determine immune response. The optimum dosage of antigen of the device could be determined by developing dose response curves at appropriate

time intervals post implantation. Similarly, the cell population in the device could be determined at appropriate intervals (e.g. days 3, 7, 10 etc.) to verify the migration of cells into the device, cell types in the device and optimum configuration of holes etc. to provide the most advantageous conditions for immune modulation in any animal with a  
5 particular antigen (or antigens).

We Claim:

1. An immune modulation device that is suitable for use in modulating an immune response in animals, comprising an impermeable biocompatible shell having an outer surface with plurality of pores of suitable size to allow the ingress and egress of immune cells and said impermeable biocompatible shell having an interior lumen, a biocompatible fibrous scaffolding being disposed within said interior lumen.
2. The immune modulation device of claim 1 wherein the fibrous scaffolding has a porosity of from about 25 percent to about 95 percent.
3. The immune modulation device of claim 1 wherein the fibrous scaffolding is made from filaments with a diameter of less than 20 microns.
4. The immune modulation device of claim 1 wherein the fibrous scaffolding is made from filaments with a denier of from about 0.2 to about 10.
5. The immune modulation device of claim 1 wherein the fibrous scaffolding is made from filaments with a denier of from about 0.8 to about 6.
6. The immune modulation device of claim 1 wherein the fibrous scaffolding is made from a bundle of filaments having a total denier of from about 20 to about 400 denier.
7. The immune modulation device of claim 1 wherein the fibrous scaffold is made from a textured yarn.
8. The immune modulation device of claim 7 wherein the textured yarn is selected from the group consisting of bulked yarns, coil yarns, core bulked yarns, crinkle yarns, entangled yarns, modified stretch yarns, nontorqued yarns, set yarns, stretch yarns and torqued yarns and combinations thereof.

9. The immune modulation device of claim 1 wherein the immune modulation device has a three dimensional shape selected from the group consisting of spherical, cylindrical, rectangular and rhomboidal.
- 5 10. The immune modulation device of claim 8 wherein the immune modulation device is cylindrical in shape.
11. The immune modulation device of claim 10 wherein the cylindrically shaped immune modulation device has an outer diameter of less than 1 millimeter.
- 10 12. The immune modulation device of claim 11 wherein the cylindrically shaped immune modulation device has an outer diameter of less than 750 microns.
13. The immune modulation device of claim 10 wherein the cylindrically shaped immune modulation device has a wall thickness of less than 250 microns.
- 15 14. The immune modulation device of claim 13 wherein the cylindrically shaped immune modulation device has a wall thickness of less than 150 microns.
- 20 15. The immune modulation device of claim 1 wherein the pores on the outer surface of the immune modulation device comprise less than 25 percent of the outer surface.
16. The immune modulation device of claim 15 wherein the pores range in size 25 from about 10 to about 500 microns.
17. The immune modulation device of claim 1 wherein the immune modulation device is bioabsorbable.
- 30 18. The immune modulation device of claim 17 wherein the bioabsorbable immune modulation device is made from a polymer selected from the group consisting of aliphatic polyesters, poly(amino acids), copoly(ether-esters), polyalkylenes oxalates, polyamides, tyrosine derived polycarbonates, poly(iminocarbonates), polyorthoesters,

polyoxaesters, polyamidoesters, polyoxaesters containing amine groups, poly(anhydrides), polyphosphazenes, biomolecules and blends thereof.

19. The immune modulation device of claim 18 wherein the bioabsorbable immune  
5 modulation device is made from an aliphatic polyester.

20. The immune modulation device of claim 19 wherein the aliphatic polyester is  
selected from the group consisting of homopolymers and copolymers of lactide (which  
includes lactic acid, D-, L- and meso lactide), glycolide (including glycolic acid), ε-  
10 caprolactone, p-dioxanone (1,4-dioxan-2-one), trimethylene carbonate (1,3-dioxan-2-  
one), alkyl derivatives of trimethylene carbonate, delta-valerolactone, beta-  
butyrolactone, gamma-butyrolactone, ε-decalactone, hydroxybutyrate, hydroxyvalerate,  
1,4-dioxepan-2-one (including its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione),  
1,5-dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one, 2,5-diketomorpholine,  
15 pivalolactone, gamma, gamma-diethylpropiolactone, ethylene carbonate, ethylene  
oxalate, 3-methyl-1,4-dioxane-2,5-dione, 3,3-diethyl-1,4-dioxan-2,5-dione, 6,8-  
dioxabicyclooctane-7-one and polymer blends thereof.

21. The immune modulation device of claim 20 wherein the shell is made from an  
20 aliphatic polyester selected from the group consisting of homopolymers and  
copolymers of lactide (which includes lactic acid, D-, L- and meso lactide), glycolide  
(including glycolic acid), ε-caprolactone, p-dioxanone (1,4-dioxan-2-one), trimethylene  
carbonate (1,3-dioxan-2-one), alkyl derivatives of trimethylene carbonate, 1,4-  
25 dioxepan-2-one (including its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione), 1,5-  
dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one and polymer blends thereof.

22. The immune modulation device of claim 20 wherein the shell is made from an  
aliphatic polyester selected from the group consisting of poly(p-dioxanone), glycolide-  
co-ε-caprolactone, glycolide-co-trimethylene carbonate, glycolide-co-1,5-dioxepan-2-  
30 one, 6,6-dimethyl-1,4-dioxan-2-one and blends thereof.

23. The immune modulation device of claim 1 wherein the biocompatible fibrous  
scaffolding is made from an aliphatic polyester selected from the group consisting of

homopolymers and copolymers of lactide (which includes lactic acid, D-, L- and meso lactide), glycolide (including glycolic acid),  $\epsilon$ -caprolactone, p-dioxanone (1,4-dioxan-2-one), trimethylene carbonate (1,3-dioxan-2-one), alkyl derivatives of trimethylene carbonate, 1,4-dioxepan-2-one (including its dimer 1,5,8,12-tetraoxacyclotetradecane-7,14-dione), 1,5-dioxepan-2-one, 6,6-dimethyl-1,4-dioxan-2-one and polymer blends thereof.

24. The immune modulation device of claim 23 wherein the biocompatible fibrous scaffolding is made from an aliphatic polyester selected polyglycolide, poly(p-dioxanone), glycolide-co- $\epsilon$ -caprolactone, glycolide-co-trimethylene carbonate and glycolide-co-lactide.

25. The immune modulation device of claim 1 wherein the shell is made from poly(p-dioxanone) and the fibrous scaffolding is made from a copolymer of about 90 weight percent glycolide and about 10 weight percent lactide.

26. The immune modulation device of claim 25 wherein the fibrous scaffolding is made from a textured yarn.

27. The immune modulation device of claim 1 wherein the shell is made from a copolymer of from about 35 to about 45 weight percent epsilon-caprolactone and from about 55 to about 65 weight percent glycolide and the fibrous scaffolding is made from a copolymer of about 90 weight percent glycolide and about 10 weight percent lactide.

28. The immune modulation device of claim 27 wherein the fibrous scaffolding is made from a textured yarn.

29. The immune modulation device of claim 1 which contains one or more antigens.

30. The immune modulation device of claim 29 wherein the antigen is selected from the group of natural antigens, synthetic antigens and combinations thereof.

31. The immune modulation device of claim 30 wherein the natural antigen is derived from a microbe selected from the group consisting of *Actinobacillus equuli*, *Actinobacillus lignieresii*, *Actinobacillus seminis*, *Aerobacter aerogenes*, *Borrelia burgdorferi*, *Babesia microti*, *Klebsiella pneumoniae*, *Bacillus cereus*, *Bordetella pertussis*, *Brucella abortus*, *Brucella melitensis*, *Brucella ovis*, *Brucella suis*, *Brucella canis*, *Campylobacter fetus*, *Campylobacter fetus intestinalis*, *Chlamydia psittaci*, *Chlamydia trachomatis*, *Clostridium tetani*, *Corynebacterium acne* Types 1 and 2, *Corynebacterium diphtheriae*, *Corynebacterium equi*, *Corynebacterium pyogenes*, *Corynebacterium renale*, *Coxiella burnetii*, *Diplococcus pneumoniae*, *Escherichia coli*, *Ehrlichia phagocytophila*, *Ehrlichia equi*, *Fusobacterium necrophorum*, *Granuloma inguinale*, *Haemophilus influenzae*, *Haemophilus vaginalis*, Group b *Hemophilus ducreyi*, *Lymphopathia venereum*, *Leptospira pomona*, *Listeria monocytogenes*, *Microplasma hominis*, *Moraxella bovis*, *Mycobacterium tuberculosis*, *Mycobacterium laprae*, *Mycoplasma bovigenitalium*, *Neisseria gonorrhoea*, *Neisseria meningitidis*, *Pseudomonas maltophilia*, *Pasteurella multocida*, *Pasteurella haemolytica*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Rickettsia prowazekii*, *Rickettsia mooseri*, *Rickettsia rickettsii*, *Rickettsia tsutsugamushi*, *Rickettsia akari*, *Salmonella abortus ovis*, *Salmonella abortus equi*, *Salmonella dublin*, *Salmonella enteritidis*, *Salmonella heidelberg*, *Salmonella paratyphi*, *Salmonella typhimurium*, *Shigella dysenteriae*, *Staphylococcus aureus*, *Streptococcus ecoli*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*, *Streptococcus mutans*, *Streptococcus Group B*, *Streptococcus bovis*, *Streptococcus dysgalactiae*, *Streptococcus equisimili*, *Streptococcus uberis*, *Streptococcus viridans*, *Treponema pallidum*, *Vibrio cholerae*, *Yersina pesti*, *Yersinia enterocolitica*, *Aspergillus fumigatus*, *Blastomyces dermatitidis*, *Candida albicans*, *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, influenza viruses, HIV, human papilloma virus, cytomegalovirus, polio virus, rabies virus, Equine herpes virus, Equine arteritis virus, IBR--IBP virus, BVD--MD virus, Herpes virus (humonis types 1 and 2), *Schistosoma*, *Plasmodium*, *Onchocerca*, parasitic amoebas and combination thereof.
32. A method of modulating the immune system in an animal to an antigen by implanting within the body of said animal an immune modulation device comprising an impermeable biocompatible shell having an outer surface with plurality of pores of

suitable size to allow the ingress and egress of immune cells and said impermeable biocompatible shell having an interior lumen, a biocompatible fibrous scaffolding being disposed within said interior lumen, said interior lumen containing a quantity of antigen sufficient to provoke an immune response.

5

33. The method of claim 32 wherein the antigen is bioavailable at the time the immune modulation device is implanted into said animal.

10

34. The method of claim 32 wherein the antigen becomes bioavailable after the immune modulation device is implanted into said animal.

15

35. The method of claim 32 wherein the quantity of antigen and the timing of the bioavailability of said antigen within the immune modulation device relative to the time of implantation of the immune modulation device into said animal results in inducing or enhancing the immune response to said antigen.

20

36. The method of claim 32 wherein the quantity of antigen and the timing of the bioavailability of said antigen within said immune modulation device relative to the time of implantation of said immune modulation device into said animal is sufficient to result in suppressing or down regulating an existing or potential immune response to said antigen.

25

37. The method of claim 32 wherein multiple antigens are present in the device in amounts sufficient to provoke an immune response.

30

38. The method of claim 32 wherein only a portion of the antigen is bioavailable at a time the immune modulation device is implanted.

39. The method of claim 37 wherein only a portion of the multiple antigens are bioavailable at a time the immune modulation device is implanted.

40. The method of claim 32 wherein only a portion of the antigen is bioavailable at 3 days after implantation of the immune modulation device.

41. A method of obtaining immune cells from an animal comprising harvesting immune cells from an immune modulation device comprised of an impermeable biocompatible shell having an outer surface with plurality of pores of suitable size to allow the ingress and egress of immune cells and said impermeable biocompatible shell having an interior lumen, a biocompatible fibrous scaffolding being disposed within said interior lumen, said interior lumen having therein a quantity of antigen or chemotactic agent sufficient to provoke an immune response that was implanted within an animal time sufficient to allow immune cells to migrate into the immune modulation device.

10 42. The method of claim 41 wherein the harvested cells are reintroduced to animals.

15 43. A method of manufacturing an immune modulation device having an impermeable biocompatible shell having an outer surface and an interior lumen comprising

20 placing a fibrous scaffolding within an interior lumen of the impermeable biocompatible shell; and

25 forming pores within said biocompatible impermeable shell of suitable size to allow the ingress and egress of immune cells.

44. The method of claim 43 wherein the biocompatible impermeable shell has a cylindrical shape having a first end and a second end.

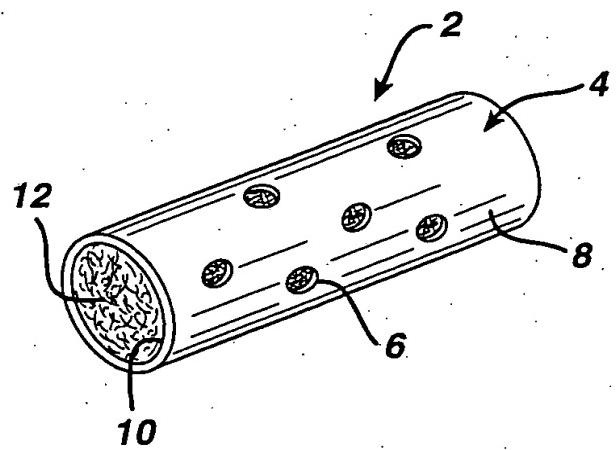
45. The method of claim 44 wherein the first end of the biocompatible impermeable shell is sealed.

30 46. The method of claim 45 wherein the end is sealed after the fibrous scaffolding is placed within the biocompatible impermeable shell.

47. The method of claim 46 wherein the biocompatible impermeable shell is made of a polymer.
48. The method of claim 47 wherein the end of the biocompatible impermeable shell is crimped and heated to seal said first end.
- 5
49. The method of claim 43 wherein at least one antigen is inserted within the interior lumen in an amount sufficient to provoke an immune response.
- 10 50. The immune modulation device of claim 43 wherein the pores are formed by laser ablation.
51. The immune modulation device of claim 43 wherein the impermeable biocompatible shell having an outer surface and an interior lumen is formed by extruding a biocompatible polymer.
- 15
52. The immune modulation device of claim 10 wherein the cylinder has a first end and a second end, said first end being sealed.

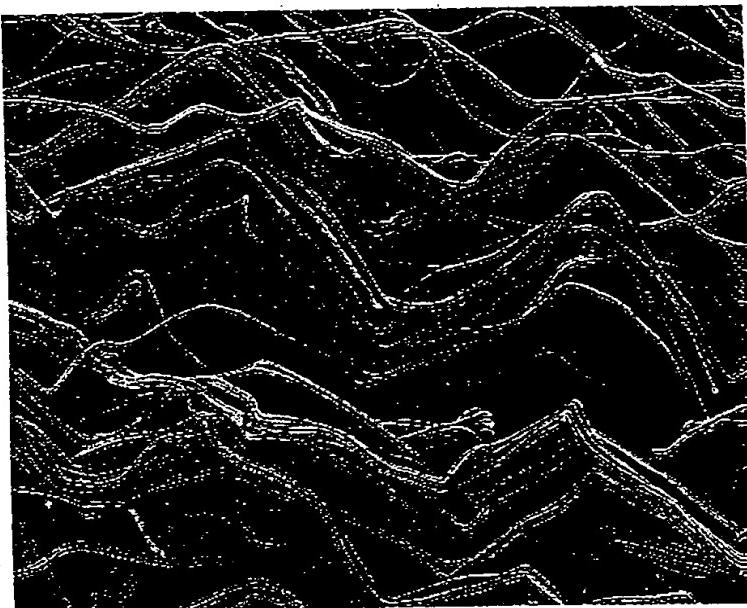
### **Abstract of the Disclosure**

The present invention is directed to an implantable immune modulation device that is useful for modulating an immune response in mammals, comprising a plurality of fibers, within a porous shell. The fiber filling is loaded with single or multiple antigens, and optionally one or more biologically active compounds such as cytokines (e.g. lymphokines, chemokines etc.); attachment factors, genes, peptides, proteins, nucleotides, carbohydrates or cells depending on the application.

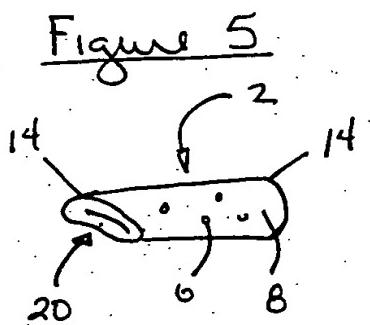
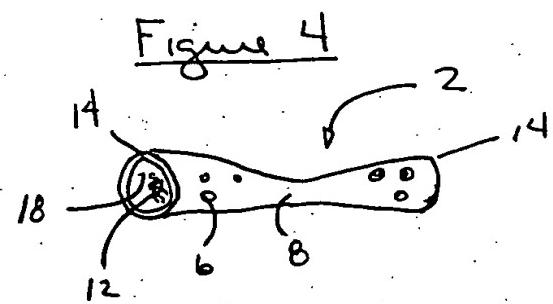
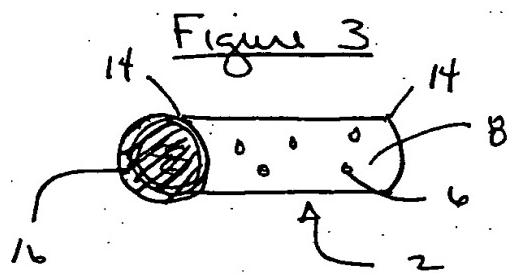
**FIG. 1**

2/3

**FIG. 2**



x50 500 $\mu$ n





Pennie & Edmonds LLP  
ATTORNEYS - AT - LAW

NEW YORK  
1155 AVENUE OF THE AMERICAS  
NEW YORK, NY 10036 -2711  
(212) 790-9090  
FACSIMILE: (212) 869-8864/9741

WASHINGTON, D.C.  
1667 K STREET, N.W.  
WASHINGTON, D.C. 20006-1605  
(202) 496-4400  
FACSIMILE: (202) 496-4444

PALO ALTO  
3300 HILLVIEW AVENUE  
PALO ALTO, CALIFORNIA 94304-1203  
(650) 493-4935  
FACSIMILE (650) 493-5556

WRITER'S DIRECT DIAL:  
(212) 790-6447  
INTERNET ADDRESS:  
[RYANM@PENNIE.COM](mailto:RYANM@PENNIE.COM)

May 28, 2002

***Via Certified Mail – Return Receipt Requested***

Our Ref. No.: 10162-0006-999

Mr. Kevor S. TenHuisen  
40 Alexandra Way  
Clinton, New Jersey 08809

Re: U.S. Patent Application Serial No. 10/017,457  
Filed: December 7, 2001  
For: IMMUNE MODULATION DEVICE FOR USE IN ANIMALS  
By: A. Cerami, C. Cerami, Q. Xie, K. TenHuisen, J. Rosenblatt and I. Koyfman

Dear Mr. TenHuisen:

Enclosed for your records is a copy of the Filing Receipt and a copy of the License for Foreign Filing that were mailed March 21, 2002, from the U.S. Patent and Trademark Office in connection with the above-identified nonprovisional patent application. The Filing Receipt confirms the filing date and serial number for the above-captioned patent application.

Also enclosed is a copy of a Notice to File Missing Parts of Nonprovisional Application. This Notice indicates that an executed Declaration must be filed.

Accordingly, please review the enclosed copy of the above-identified patent application, as filed, and then sign and date the enclosed Declaration and Power of Attorney. Once you have done so, please return the executed Declaration and Power of Attorney to us for filing with the U.S. Patent and Trademark Office in response to the Notice to File Missing Parts.

Since the above identified-application will claim priority to the U.S. non-provisional patent application filed on May 11, 2001, which is directed to the same invention, we would appreciate it if you would provide us with a copy of the filling receipt or at least the application serial number for the provisional application.

Mr. Kevor S. TenHuisen  
May 28, 2002  
Page 2

Thank you for your assistance in this matter. Should you have any questions regarding the above, please do not hesitate to contact us.

Sincerely,

  
Michael J. Ryan

Enclosures

cc: Mr. Joel Rosenblatt (w/encs)  
Ms. Ilya S. Koyfman (w/encs)  
Anthony Cerami, Ph.D.  
Carla Cerami, M.D., Ph.D.  
Qiao-wen Xie, Ph.D.  
Hal Brent Woodrow, Esq. (w/o encs)  
Laura A. Coruzzi, Esq.



Mr. Kevor S. TenHuisen  
May 28, 2002  
Page 3

bc: Ann L. Gisolfi, Esq.

**SENDER: COMPLETE THIS SECTION**

- Complete items 1, 2, and 3. Also complete item 4 if Restricted Delivery is desired.
- Print your name and address on the reverse so that we can return the card to you.
- Attach this card to the back of the mailpiece, or on the front if space permits.

1. Article Addressed to:

**Mr. Kevor S. TenHuisen  
40 Alexandra Way  
Clinton, NJ 08809**

2. Article Number

(Transfer from service label)

**7099 3400 0017 1340 3096****COMPLETE THIS SECTION ON DELIVERY**

A. Signature

**X**
 Agent  
 Addressee

B. Received by (Printed Name)

C. Date of Delivery

D. Is delivery address different from item 1?  YesIf YES, enter delivery address below:  No

3. Service Type

<input checked="" type="checkbox"/> Certified Mail	<input type="checkbox"/> Express Mail
<input type="checkbox"/> Registered	<input checked="" type="checkbox"/> Return Receipt for Merchandise
<input type="checkbox"/> Insured Mail	<input type="checkbox"/> C.O.D.

4. Restricted Delivery? (Extra Fee)  Yes

PS Form 3811, August 2001

Domestic Return Receipt

102595-01-M-2509

PLACE STICKER AT TOP OF ENVELOPE  
TO THE RIGHT OF RETURN ADDRESS.  
FOLD AT DOTTED LINE**CERTIFIED MAIL**
 7099 3400 0017 1340 3096  
 7099 3400 0017 1340 3096  
 7099 3400 0017 1340 3096

**U.S. Postal Service  
CERTIFIED MAIL RECEIPT**  
*(Domestic Mail Only; No Insurance Coverage Provided)*
**10162-006 MJR/NMoore**

Postage	\$
Certified Fee	
Return Receipt Fee (Endorsement Required)	
Restricted Delivery Fee (Endorsement Required)	
Total Postage & Fees	\$

Postmark  
Here

Recipient's Name (Please Print Clearly) (to be completed by mailer)

**Mr. Kevor S. TenHuisen**

Street, Apt. No., or PO Box No.

**40 Alexandra Way**City, State, ZIP+4  
**Clinton, NJ 08809**

PS Form 3800, February 2000

See Reverse for Instructions

## DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below at 201 et seq. underneath my name.

I believe I am the original, first and sole inventor if only one name is listed at 201 below, or an original, first and joint inventor if plural names are listed at 201 et seq. below, of the subject matter which is claimed and for which a patent is sought on the invention entitled

## IMMUNE MODULATION DEVICE FOR USE IN ANIMALS

and for which a patent application:

- is attached hereto and includes amendment(s) filed on *(if applicable)*
- was filed in the United States on December 7, 2001 as Application No. 10/017,457 *(for declaration not accompanying application)*  
with amendment(s) filed on *(if applicable)*
- was filed as PCT international Application No.   on   and was amended under PCT Article 19 on *(if applicable)*

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED PRIOR TO THE FILING DATE OF THE APPLICATION			
APPLICATION NUMBER	COUNTRY	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
			YES <input type="checkbox"/> NO <input type="checkbox"/>
			YES <input type="checkbox"/> NO <input type="checkbox"/>

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

APPLICATION NUMBER	FILING DATE
60/****,***	May 11, 2001

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	FILING DATE	STATUS		
		PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint Berj A. Terzian (Reg. No. 20060), David Weild, III (Reg. No. 21094), Barry D. Rein (Reg. No. 22411), Stanton T. Lawrence, III (Reg. No. 25736), Charles E. McKenney (Reg. No. 22795), Philip T. Shannon (Reg. No. 24278), Francis E. Morris (Reg. No. 24615), Charles E. Miller (Reg. No. 24576), Gidon D. Stern (Reg. No. 27469), John J. Lauter, Jr. (Reg. No. 27814), Brian M. Poissant (Reg. No. 28462), Brian D. Coggio (Reg. No. 27624), Rory J. Radding (Reg. No. 28749), Stephen J. Harbulak (Reg. No. 29166), Donald J. Goodell (Reg. No. 19766), Thomas E. Friebel (Reg. No. 29258), Laura A. Coruzzi (Reg. No. 30742), Jennifer Gordon (Reg. No. 30753), Geraldine F. Baldwin (Reg. No. 31232), Victor N. Balancia (Reg. No. 31231), Samuel B. Abrams (Reg. No. 30605), Steven I. Wallach (Reg. No. 35402), Marcia H. Sundeen (Reg. No. 30893), Paul J. Zegger (Reg. No. 33821), Edmond R. Bannon (Reg. No. 32110), Bruce J. Barker (Reg. No. 33291), Adriane M. Antler (Reg. No. 32605), Thomas G. Rowan (Reg. No. 34419), James G. Markey (Reg. No. 31636), Thomas D. Kohler (Reg. No. 32797), Scott D. Stimpson (Reg. No. 33607), Gary S. Williams (Reg. No. 31066), Ann L. Gisolfi (Reg. No. 31956), Todd A. Wagner (Reg. No. 35399), Scott B. Familiant (Reg. No. 35514), Kelly D. Talcott (Reg. No. 39582), Francis D. Cerrito (Reg. No. 38100), Anthony M. Insogna (Reg. No. 35203), Brian M. Rothery (Reg. No. 35340), Brian D. Siff (Reg. No. 35679), Michael J. Lyons (Reg. No. 37386), Garland T. Stephens (Reg. No. 37242), William J. Sipio (Reg. No. 34514), Nikolaos C. George (Reg. No. 39201), Stephen S. Rabinowitz (Reg. No. 40286), Ognjan V. Shentov (Reg. No. 38051), and Kenneth L. Stein (Reg. No. 38704), all of Pennie & Edmonds LLP, whose addresses are 1155 Avenue of the Americas, New York, New York 10036, 1667 K Street N.W., Washington, DC 20006 and 3300 Hillview Avenue, Palo Alto, CA 94304, and each of them, my attorneys, to prosecute this application, and to transact all business in the Patent and Trademark Office connected therewith.

SEND CORRESPONDENCE TO:		PENNIE & EDMONDS LLP 1155 Avenue of the Americas New York, N.Y. 10036-2711 PTO Customer No. 20583		DIRECT TELEPHONE CALLS TO: PENNIE & EDMONDS LLP DOCKETING (212) 790-2803	
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.					
2 0 1	FULL NAME OF INVENTOR	LAST NAME Cerami	FIRST NAME Anthony	MIDDLE NAME	
	RESIDENCE & CITIZENSHIP	CITY Sleepy Hollow	STATE OR FOREIGN COUNTRY New York	COUNTRY OF CITIZENSHIP United States	
	POST OFFICE ADDRESS	STREET 121 Farrington Avenue	CITY Sleepy Hollow	STATE OR COUNTRY New York	ZIP CODE 10591
	SIGNATURE OF INVENTOR 201			DATE	
2 0 2	FULL NAME OF INVENTOR	LAST NAME Cerami	FIRST NAME Carla	MIDDLE NAME	
	RESIDENCE & CITIZENSHIP	CITY Sleepy Hollow	STATE OR FOREIGN COUNTRY New York	COUNTRY OF CITIZENSHIP United States	
	POST OFFICE ADDRESS	STREET 121 Farrington Avenue	CITY Sleepy Hollow	STATE OR COUNTRY New York	ZIP CODE 10591
	SIGNATURE OF INVENTOR 202			DATE	
2 0 3	FULL NAME OF INVENTOR	LAST NAME Xie	FIRST NAME Qiao-wen	MIDDLE NAME	
	RESIDENCE & CITIZENSHIP	CITY Yonkers	STATE OR FOREIGN COUNTRY New York	COUNTRY OF CITIZENSHIP United States	
	POST OFFICE ADDRESS	STREET 30 Sidehill Lane	CITY Yonkers	STATE OR COUNTRY New York	ZIP CODE 10710
	SIGNATURE OF INVENTOR 203			DATE	
2 0 4	FULL NAME OF INVENTOR	LAST NAME TenHuisen	FIRST NAME Kevor	MIDDLE NAME S.	
	RESIDENCE & CITIZENSHIP	CITY Clinton	STATE OR FOREIGN COUNTRY New Jersey	COUNTRY OF CITIZENSHIP United States	
	POST OFFICE ADDRESS	STREET 40 Alexandra Way	CITY Clinton	STATE OR COUNTRY New Jersey	ZIP CODE 08809
	SIGNATURE OF INVENTOR 204			DATE	
2 0 5	FULL NAME OF INVENTOR	LAST NAME Rosenblatt	FIRST NAME Joel	MIDDLE NAME	
	RESIDENCE & CITIZENSHIP	CITY Watchung	STATE OR FOREIGN COUNTRY New Jersey	COUNTRY OF CITIZENSHIP United States	
	POST OFFICE ADDRESS	STREET 47 Robin Glen Road	CITY Watchung	STATE OR COUNTRY New Jersey	ZIP CODE 07060
	SIGNATURE OF INVENTOR 205			DATE	

2 0 6	FULL NAME OF INVENTOR	LAST NAME Koyfinan	FIRST NAME Ilya	MIDDLE NAME S.	
	RESIDENCE & CITIZENSHIP	CITY Ringoess	STATE OR FOREIGN COUNTRY New Jersey	COUNTRY OF CITIZENSHIP United States	
	POST OFFICE ADDRESS	STREET 5 Messenger Lane	CITY New Jersey	STATE OR COUNTRY New Jersey	ZIP CODE 08551
		SIGNATURE OF INVENTOR 206			DATE

## **EXHIBIT B**



Johnson & Johnson

10160-005

OFFICE OF  
GENERAL COUNSEL

ONE JOHNSON & JOHNSON PLAZA  
NEW BRUNSWICK, N.J. 08933-7003

June 19, 2002

Michael J. Ryan, Esquire  
**Pennie & Edmonds, LLP**  
1155 Avenue of The Americas  
New York, NY 10036

**Re: U.S. Patent Application Serial No. 10/017,457**  
**Immune Modulation Device for Use in Animals**  
**Our Docket No.: ORT1295**

Dear Mr. Ryan:

I am in receipt of your letter to Messieurs TenHuisen, Rosenblatt and Koyfman dated May 28, 2002. Included therein were a copy of United States Patent Application Serial No. 10/017,457, filed by yourself and Ms. Coruzzi, and Declaration and Power of Attorney regarding the application prepared by your firm for execution by each individual.

Initially, as you most certainly must be aware, all of the above individuals are employees of Ethicon, Inc. and are duly represented by counsel. Contact of these individuals by your firm is improper and we must insist that you refrain from making any further contact with any Ethicon employees.

In addition, no representative of Pennie and Edmonds has the authority to represent either the individuals or Johnson & Johnson affiliates in this matter. The Declarations and Power of Attorney will not be executed.

As both the Cerami's and Ms. Coruzzi are aware, prior to filing our application to which US 10/017,457 claims priority, and which is substantially identical to US 10/017,457, Mr. Woodrow gave the Cerami's and Ms. Xie ample opportunity to provide corroborated evidence of their claim to inventorship with respect to claims filed in our application. The Cerami's and Ms. Xie simply refused or were unable to allege any facts or provide any evidence to support any such claim. Our records do not reflect any information that

Michael J. Ryan, Esquire

2.

June 19, 2002

would support the claim to inventorship by the Cerami's or Ms. Xie. To date, we still have no reason to believe that either the Cerami's or Ms. Xie are rightful inventors to any claims of US 10/017,457 or our application to which it claims priority. Consequently, we believe that the inventorship you have listed in US 10/017,457 is inaccurate and the claim to priority improper.

Any future correspondence regarding this matter should be directed to my attention.

Very truly yours,

Johnson & Johnson

  
Kent Wissing

WKW/c

CC: M. S. Goodwin  
I. S. Koyfman  
J. Rosenblatt  
K. TenHuisen  
H. B. Woodrow

*Johnson & Johnson*

10162-005-

OFFICE OF  
GENERAL COUNSEL

ONE JOHNSON & JOHNSON PLAZA  
NEW BRUNSWICK, N.J. 08933-7003

March 15, 2002

Ann L. Gisolfi, Esq.  
Pennie & Edmonds LLP  
1155 Avenue of the Americas  
New York, NY 10036-2711

Re: Inventorship Investigation of pending U.S. Patent Appln. for  
IMMUNE MODULATION DEVICE FOR USE IN ANIMALS  
Our Ref. 1012-81

Dear Ms. Gisolfi:

I am in receipt of your letter of January 18, 2002.

As you are aware, I have had our records searched again, at your request to see if we possessed any information that would support your clients allegations of joint inventorship by the Ceramis or their employees on the above-identified application. That search, as I informed you by phone on January 15<sup>th</sup>, did not result in the location of any information that would support your client's allegations of joint inventorship on the above-identified application.

I have on numerous occasions requested that you or your clients provide some corroborated information that would support your allegations that the Ceramis or their employees are joint inventors on the above-identified application. However, despite my repeated requests, no information has been provided that would support your allegation of joint inventorship. Therefore, I have no basis to add any additional inventors to the above-identified patent application.

Please address all future correspondence on this issue to my associate Kent Wissing, Esq. (732-524-6201).

Very truly yours,  
*Hal B. Woodrow*  
Hal B. Woodrow

HBW/rb  
cc: Kent Wissing, Esq.



NEW YORK  
1155 AVENUE OF THE AMERICAS  
NEW YORK, NY 10036-2711  
(212) 790-9090  
FACSIMILE: (212) 869-8864/9741

WASHINGTON, D.C.  
1667 K STREET, N.W.  
WASHINGTON, D.C. 20006-1605  
(202) 496-4400  
FACSIMILE: (202) 496-4444

January 18, 2002

By Telefacsimile and First Class Mail

010162-0005-999

Hal B. Woodrow, Esq.  
Johnson & Johnson  
One Johnson & Johnson Plaza  
New Brunswick, New Jersey 08933-7003

WRITER'S DIRECT DIAL:  
(212) 790-6413  
INTERNET ADDRESS:  
[GISOLFIA@PENNIE.COM](mailto:GISOLFIA@PENNIE.COM)

Re: Inventorship Investigation of pending U.S. Patent Application entitled  
IMMUNE MODULATION DEVICE FOR USE IN ANIMALS

Dear Hal:

Frankly, I was surprised by your January 15<sup>th</sup> voicemail message that you believe that you are able to conduct an inventorship investigation based on only one side of the story. As you are well aware, an issue has been raised about the correctness of the inventive entity identified by Ethicon on the above-identified application. Also, as you are aware, and I quote from your August 24, 2001 letter to Laura Coruzzi,

"the laws governing joint inventorship are embodied in 35 USC 116. Willful failure to comply with this statute may result in the invalidation of the subsequently issuing patent. Additionally, patent attorneys have an ethical duty to inquire into the inventorship of an invention before filing a patent application to assure that the inventorship, based on the facts, appears correct."

With this in mind, as well as the outstanding issue as to the correctness of the inventive entity, I have repeatedly urged that we either meet or arrange for some exchange of relevant documents supporting inventorship by the Cerami participants, as well as those Ethicon employees already named as inventors. In this way we, as patent attorneys, can be certain that we have fully investigated inventorship as is required by the patent laws.

You continue to suggest that it is our burden to provide you with information on our client's contribution to the invention for your independent review and conclusion. Yet, you are unwilling to provide us with any information supporting the contribution of the Ethicon inventors. We remain willing to exchange information, or better yet, to arrange a meeting where all concerned can have a full and frank discussion of how and by whom the invention was made.



Pennie & Edmonds LLP  
ATTORNEYS AT LAW

Hal B. Woodrow, Esq.

January 18, 2002

Page 2

Accordingly, I disagree with your conclusion that you are "confined to going ahead as we are", and without more information from you, I cannot agree that inventorship by solely Ethicon personnel is correct.

Very truly yours,

A handwritten signature in black ink, appearing to read "Ann L. Gisola".

cc: Dr. Anthony Cerami  
Dr. Carla Cerami  
Dr. Michael Ryan  
Laura A. Coruzzi, Esq.



Pennie & Edmonds LLP  
ATTORNEYS AT LAW

NEW YORK  
1155 AVENUE OF THE AMERICAS  
NEW YORK, NY 10036 -2711  
(212) 790-9090  
FACSIMILE: (212) 869-8864/9741

WASHINGTON, D.C.  
1667 K STREET, N.W.  
WASHINGTON, D.C. 20006 -1605  
(202) 496-4400  
FACSIMILE: (202) 496-4444

PALO ALTO  
3300 HILLVIEW AVENUE  
PALO ALTO, CALIFORNIA 94304 -1203  
(650) 493-4935  
FACSIMILE (650) 493-5556

WRITER'S DIRECT DIAL:  
(212) 790-6413  
INTERNET ADDRESS:  
GISOLFIA@PENNIE.COM

010162-0005-999

December 13, 2001

By Telefacsimile and First Class Mail

Hal B. Woodrow, Esq.  
Johnson & Johnson  
One Johnson & Johnson Plaza  
New Brunswick, New Jersey 08933-7003

Re: Inventorship Investigation of pending U.S. Patent Application entitled  
IMMUNE MODULATION DEVICE FOR USE IN ANIMALS

Dear Hal:

It has been several weeks since we last spoke concerning the conduct of an inventorship investigation in connection with subject matter described and claimed in the above-identified application filed by Ethicon. By way of reminder, I urged that we explore the contributions to the invention made by certain Cerami personnel, as well as the contributions made by Kevor S. TenHuisen, Joel Rosenblatt and Ilya S. Koifman, who are the only inventors named on such application. As we discussed, I understand that the invention was made in the conduct of a collaboration between VLN, LLC and Ethicon and that contributions were made by employees of both parties.

Please advise when we can arrange for a meeting with all necessary parties in attendance so that, as required by the patent laws, the true inventors are named. As so much time has passed, I hope that we address this matter quickly.

Very truly yours,

A handwritten signature in black ink, appearing to read "Ann L. Gisolfi".

cc: Dr. Anthony Cerami  
Dr. Carla Cerami  
Dr. Michael Ryan  
Laura A. Coruzzi, Esq.

# PENNIE & EDMONDS LLP

WASHINGTON OFFICE  
1667 K STREET, N.W.  
WASHINGTON, DC 20006  
(202) 496-4400  
FACSIMILE: (202) 496-4444

1155 AVENUE OF THE AMERICAS  
NEW YORK, NY 10036-2711  
(212) 790-9090  
FACSIMILE: (212) 869-9741/8864  
MCIMAIL: 561-3768

CALIFORNIA OFFICE  
3300 HILLVIEW AVENUE  
PALO ALTO, CALIFORNIA 94304  
(650) 493-4933  
FACSIMILE: (650) 493-5556

ANN L. GISOLFI DIRECT DIAL:  
(212) 790-6413

INTERNET ADDRESS  
GISOLFIA@PENNIE.COM

September 24, 2001

By Telefacsimile and First Class Mail

005

010162-0002-999

Hal B. Woodrow, Esq.  
Johnson & Johnson  
One Johnson & Johnson Plaza  
New Brunswick, New Jersey 08933-7003

Re: Inventorship of the Provisional Patent Application for IMMUNE  
MODULATION DEVICE FOR USE IN ANIMALS  
Your Ref.: 1012.81

Dear Hal:

Confirming our telephone discussion on Friday, September 21, 2001, we are in the process of assembling information establishing that the above-identified invention was made jointly with Cerami inventors. As discussed, we expect to provide that information by the end of October.

Very truly yours,

  
Ann L. Gisolfi

cc: Laura A. Coruzzi, Esq.

10162-~~7~~  
J, Te 005

# Johnson & Johnson

OFFICE OF  
GENERAL COUNSEL

ONE JOHNSON & JOHNSON PLAZA  
NEW BRUNSWICK, N.J. 08933-7003

August 24, 2001

Laura A. Coruzzi  
Pennie & Edmonds LLP  
1155 Avenue of the Americas  
New York, NY 10036-2711

Re: Inventorship of the Provisional Patent Application for  
IMMUNE MODULATION DEVICE  
FOR USE IN ANIMALS  
Your Ref. 10162-002  
Our Ref. 1012.81

Dear Ms. Coruzzi:

I am in receipt of your letter of August 7, 2001 regarding the above-identified patent application, which we provided to you as a confidential document pursuant to paragraph 7.1 of the License Agreement between the parties.

As you are aware, the laws governing joint inventorship are embodied in 35 USC 116. Willful failure to comply with this statute may result in the invalidation of the subsequently issuing patent. Additionally, patent attorneys have an ethical duty to inquire into the inventorship of an invention before filing a patent application to assure that the inventorship, based on the facts, appears correct. With this in mind, I have in our previous conversation asked you repeatedly to provide facts that would substantiate your allegation that your clients are coinventors on the above-identified patent application. In all of our conversations you have alleged that your clients are joint inventors, but could not provide any facts to support your allegations. Consequently, without any facts to rely upon I have no basis to believe that your clients are joint inventor of the above-identified patent application.

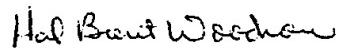
I am mindful that you have mentioned the existence of the Exclusive License Agreement between the parties in our previous discussions. However, the existence of that agreement does not establish joint inventorship. In fact the agreement anticipates that there will be separate inventions made by parties to the agreement (see paragraph 3.4). You must go beyond the existence of the agreement and provide facts to support your allegation that your clients are joint inventors.

c. Ann Gisolfi  
Mike Ryan

Since we provided you with a copy of the application on May 10, 2001, if you wish to support your assertion that your clients are coinventor, please provide corroborated facts to substantiate your claim, explaining your clients conception and pointing out your clients specific contribution to the claims in the application. Since we will begin preparations to file the nonprovisional application and foreign equivalents of the above-identified application in the near future, if you are going to present corroborated facts to support your allegations of joint inventorship you must provide that evidence to me by no later than September 30<sup>th</sup>, 2001.

We hope this letter provides you with a clear insight into how we can resolve this matter. We would be happy to meet with you and your clients in New Brunswick to resolve this issue at a mutually agreeable time. Please feel free to call me if you wish to set up a meeting to discuss this matter.

Very truly yours,



Hal B. Woodrow

HBW/rb

cc: Mr. Angelo Scopelanos  
Mr. Kenneth Berlin  
Mr. John W. Wallen  
Mr. Anthony Cerami

# PENNIE & EDMONDS LLP

WASHINGTON OFFICE  
1667 K STREET, N.W.  
WASHINGTON, DC 20006  
(202) 496-4400  
FACSIMILE: (202) 496-4444

1155 AVENUE OF THE AMERICAS  
NEW YORK, NY 10036-2711  
(212) 790-9090  
FACSIMILE: (212) 869-9741/8864  
MCI MAIL: 561-3768

CALIFORNIA OFFICE  
3300 HILLVIEW AVENUE  
PALO ALTO, CALIFORNIA 94304  
(650) 493-4935  
FACSIMILE: (650) 493-5556

WRITER'S DIRECT DIAL:  
(212) 790-6431

INTERNET ADDRESS:  
[CORUZZI@PENNIE.COM](mailto:CORUZZI@PENNIE.COM)

August 7, 2001

Via Federal Express

005

Our Ref.: 10162-002

Hal Brent Woodrow  
General Counsel  
Johnson & Johnson  
One Johnson & Johnson Plaza  
New Brunswick, NJ 08933-7003

Re: Inventorship of the Provisional Patent Application for  
IMMUNE MODULATION DEVICE FOR USE IN ANIMALS  
Filed: May 11, 2001

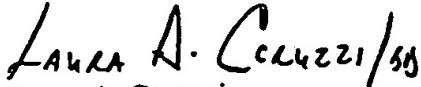
Dear Mr. Woodrow:

Thank you for your letter dated May 10, 2001, enclosing a copy of the above-identified Provisional Patent Application. We have reviewed this application along with our client and we have concluded that the invention disclosed is a product of the collaboration between our client and Johnson & Johnson scientists. Our analysis of the facts indicates that Anthony Cerami, Carla Cerami, and Qiao-wen Xie made conceptual contributions to the invention as described and claimed in the above-identified application, and should be named as co-inventors.

Therefore, please contact us at your earliest possible convenience to discuss the procedure to be used to correct the inventorship of the above-identified application to add Anthony Cerami, Carla Cerami, and Qiao-wen Xie as co-inventors.

Please be advised, that if we do not hear from you by August 31, 2001, we will be left to pursue our own recourse.

Very truly yours,

  
Laura A. Coruzzi

c: Carla Cerami, Ph.D.  
Anthony Cerami, Ph.D.  
Ann L. Gisolfi, Esq.

NY2 - 1224822.1

10162-~~005~~  
005

# Johnson & Johnson

OFFICE OF  
GENERAL COUNSEL

ONE JOHNSON & JOHNSON PLAZA  
NEW BRUNSWICK, N.J. 08933-7003

PENNIE & EDMONDS

JUN 08 2001

June 5, 2001

RECEIVED

Laura A. Coruzzi, Ph.D.  
Partner  
Pennie & Edmonds LLP  
1155 Avenue of the Americas  
New York, New York 10036

Re: Patent Application related to Exclusive License Agreement  
between VLNLLC, VLN/AVT and PRI/ OBI

Dear Laura,

Please be advised that the patent application entitled "Immune Modulation Device for Use in Animals" mailed to you on May 10, 2001 was filed and received a filing date of May 11, 2001.

This patent application should be listed as PRI/OBI Patent Rights in Exhibit C.

Yours truly,

*Hal Brent Woodrow*

Hal Brent Woodrow

File: 10162-  
PENNIE & EDMONDS 005

MAY 17 2001 2037

RECEIVED

OFFICE OF  
GENERAL COUNSEL

ONE JOHNSON & JOHNSON PLAZA  
NEW BRUNSWICK, N.J. 08933-7003

May 10, 2001

Laura A. Coruzzi, Ph.D.  
Partner  
Pennie & Edmonds LLP  
1155 Avenue of the Americas  
New York, New York 10036

Re: patent application related to Exclusive License Agreement  
between VLNLLC, VLN/AVT and PRI/ OBI

Dear Laura,

Please find enclosed a copy of Ortho Biotech Inc's confidential patent application entitled, "Immune Modulation Device for Use in Animals". This application embodies Ortho Biotech's confidential information and data related to a new design for a virtual lymph node device developed by Ortho.

The last time we spoke in August you had suggested that we consider the possibility that your clients might be joint inventors. However, no facts that would support that suggestion have ever been brought to my attention. I have discussed the invention extensively with my client, reviewed the published prior art and have found nothing that would support or substantiate your suggestion that your clients might be joint inventors. It appears from the facts that I have been able to adduce that your client performed studies on the devices supplied by Ortho using the testing procedures described in their previously published patent application. Consequently, I do not have any basis to believe that the Cerami's provided any inventive contribution to the invention described in the attached patent application.

Subsequent to our August conversation, it has come to my attention that the Cerami's have been sued by a third party in relation to the virtual lymph node. Ortho Biotech Inc., as you are undoubtedly aware has been served with a third party subpoena to produce papers. In view of this suit, I have called your office on several occasions to request assurances that our patent application would not be subject to discovery by this third party. Unfortunately, you have been unable to return my calls. Therefore, to protect my clients interests I have filed the application as a provisional patent application.

If after reviewing the invention that is being claimed in the provisional patent application you wish to bring any facts to my attention that would have a bearing on the inventorship of the invention described in the application, please contact me at 732-524-2976 so that we can discuss this issue. After I receive the filing receipt for this provisional patent application, I will inform you of the filing date so that the application can be listed as PRI/OBI Patent Rights in Exhibit C.

Sincerely yours,

Hal Brent Woodrow

Hal Brent Woodrow

NEW YORK  
1155 AVENUE OF THE AMERICAS  
NEW YORK, NY 10036 -2711  
(212) 790-9090  
FACSIMILE: (212) 869-8864/9741

WASHINGTON, D.C.  
1667 K STREET, N.W.  
WASHINGTON, D.C. 20006-1605  
(202) 496-4400  
FACSIMILE: (202) 496-4444

May 28, 2002

***Via Certified Mail -- Return Receipt Requested***

Our Ref. No.: 10162-0006-999

WRITER'S DIRECT DIAL:  
(212) 790-6447  
INTERNET ADDRESS:  
[RYANM@PENNIE.COM](mailto:RYANM@PENNIE.COM)

Ms. Ilya S. Koyfman  
5 Messenger Lane  
Ringoes, New Jersey 08551

Re: U.S. Patent Application Serial No. 10/017,457  
Filed: December 7, 2001  
For: IMMUNE MODULATION DEVICE FOR USE IN ANIMALS  
By: A. Cerami, C. Cerami, Q. Xie, K. TenHuisen, J. Rosenblatt and I. Koyfman

Dear Ms. Koyfman:

Enclosed for your records is a copy of the Filing Receipt and a copy of the License for Foreign Filing that were mailed March 21, 2002, from the U.S. Patent and Trademark Office in connection with the above-identified nonprovisional patent application. The Filing Receipt confirms the filing date and serial number for the above-captioned patent application.

Also enclosed is a copy of a Notice to File Missing Parts of Nonprovisional Application. This Notice indicates that an executed Declaration must be filed.

Accordingly, please review the enclosed copy of the above-identified patent application, as filed, and then sign and date the enclosed Declaration and Power of Attorney. Once you have done so, please return the executed Declaration and Power of Attorney to us for filing with the U.S. Patent and Trademark Office in response to the Notice to File Missing Parts.

Since the above identified-application will claim priority to the U.S. non-provisional patent application filed on May 11, 2001, which is directed to the same invention, we would appreciate it if you would provide us with a copy of the filling receipt or at least the application serial number for the provisional application.

Ms. Ilya S. Koyfman  
May 28, 2002  
Page 2

Thank you for your assistance in this matter. Should you have any questions regarding the above, please do not hesitate to contact us.

Sincerely,

  
Michael J. Ryan

Enclosures

cc: Mr. Kevor S. TenHuisen (w/encs)  
Mr. Joel Rosenblatt (w/encs)  
Anthony Cerami, Ph.D.  
Carla Cerami, M.D., Ph.D.  
Qiao-wen Xie, Ph.D.  
Hal Brent Woodrow, Esq. (w/o encs)  
Laura A. Coruzzi, Esq.



Ms. Ilya S. Koyfman  
May 28, 2002  
Page 3

bc: Ann L. Gisolfi, Esq.

**SENDER: COMPLETE THIS SECTION**

- Complete items 1, 2, and 3. Also complete Item 4 if Restricted Delivery is desired.
- Print your name and address on the reverse so that we can return the card to you.
- Attach this card to the back of the mailpiece, or on the front if space permits.

1. Article Addressed to:

Ms. Ilya S. Koyfman  
5 Messenger Lane  
Ringoes, NJ 08551

2. Article Number

(Transfer from service label)

7099 3400 0017 1340 3072

PS Form 3811, August 2001

Domestic Return Receipt

102595-01-M-2509

**COMPLETE THIS SECTION ON DELIVERY**

A. Signature

X

 Agent  
 Addressee

B. Received by (Printed Name)

C. Date of Delivery

D. Is delivery address different from item 1?  YesIf YES, enter delivery address below:  No

3. Service Type

 Certified Mail Express Mail Registered Return Receipt for Merchandise Insured Mail C.O.D.4. Restricted Delivery? (Extra Fee)  YesPLACE STICKER AT TOP OF ENVELOPE  
TO THE RIGHT OF RETURN ADDRESS.  
FOLD AT DOTTED LINE**CERTIFIED MAIL**7099 3400 0017 1340 3072  
7099 3400 0017 1340 3072  
7099 3400 0017 1340 3072  
7099 3400 0017 1340 3072**U.S. Postal Service  
CERTIFIED MAIL RECEIPT**  
(Domestic Mail Only; No Insurance Coverage Provided)

10162-006 MJR/NMoore

Postage	\$
Certified Fee	
Return Receipt Fee (Endorsement Required)	
Restricted Delivery Fee (Endorsement Required)	
Total Postage & Fees	\$

Postmark  
Here

Recipient's Name (Please Print Clearly) (to be completed by mailer)

Ms. Ilya S. Koyfman  
5 Messenger Lane  
Ringoes, NJ 08551

PS Form 3800, February 2000

See Reverse for Instructions

## DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below at 201 et seq. underneath my name.

I believe I am the original, first and sole inventor if only one name is listed at 201 below, or an original, first and joint inventor if plural names are listed at 201 et seq. below, of the subject matter which is claimed and for which a patent is sought on the invention entitled

## IMMUNE MODULATION DEVICE FOR USE IN ANIMALS

and for which a patent application:

- is attached hereto and includes amendment(s) filed on *(if applicable)*
- was filed in the United States on December 7, 2001 as Application No. 10/017,457 *(for declaration not accompanying application)* with amendment(s) filed on *(if applicable)*
- was filed as PCT international Application No. on and was amended under PCT Article 19 on *(if applicable)*

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED PRIOR TO THE FILING DATE OF THE APPLICATION			
APPLICATION NUMBER	COUNTRY	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
			YES <input type="checkbox"/> NO <input type="checkbox"/>
			YES <input type="checkbox"/> NO <input type="checkbox"/>

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

APPLICATION NUMBER	FILING DATE
60/***,***	May 11, 2001

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	FILING DATE	STATUS		
		PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint Berj A. Terzian (Reg. No. 20060), David Weild, III (Reg. No. 21094), Barry D. Rein (Reg. No. 22411), Stanton T. Lawrence, III (Reg. No. 25736), Charles E. McKenney (Reg. No. 22795), Philip T. Shannon (Reg. No. 24278), Francis E. Morris (Reg. No. 24615), Charles E. Miller (Reg. No. 24576), Gidon D. Stern (Reg. No. 27469), John J. Lauter, Jr. (Reg. No. 27814), Brian M. Poissant (Reg. No. 28462), Brian D. Coggio (Reg. No. 27624), Rory J. Radding (Reg. No. 28749), Stephen J. Harbulak (Reg. No. 29166), Donald J. Goodell (Reg. No. 19766), Thomas E. Friebel (Reg. No. 29258), Laura A. Coruzzi (Reg. No. 30742), Jennifer Gordon (Reg. No. 30753), Geraldine F. Baldwin (Reg. No. 31232), Victor N. Balancia (Reg. No. 31231), Samuel B. Abrams (Reg. No. 30605), Steven I. Wallach (Reg. No. 35402), Marcia H. Sundeen (Reg. No. 30893), Paul J. Zegger (Reg. No. 33821), Edmond R. Bannon (Reg. No. 32110), Bruce J. Barker (Reg. No. 33291), Adriane M. Antler (Reg. No. 32605), Thomas G. Rowan (Reg. No. 34419), James G. Markey (Reg. No. 31636), Thomas D. Kohler (Reg. No. 32797), Scott D. Stimpson (Reg. No. 33607), Gary S. Williams (Reg. No. 31066), Ann L. Gisolfi (Reg. No. 31956), Todd A. Wagner (Reg. No. 35399), Scott B. Familiant (Reg. No. 35514), Kelly D. Talcott (Reg. No. 39582), Francis D. Cerrito (Reg. No. 38100), Anthony M. Insogna (Reg. No. 35203), Brian M. Rothery (Reg. No. 35340), Brian D. Siff (Reg. No. 35679), Michael J. Lyons (Reg. No. 37386), Garland T. Stephens (Reg. No. 37242), William J. Sipio (Reg. No. 34514), Nikolaos C. George (Reg. No. 39201), Stephen S. Rabinowitz (Reg. No. 40286), Ognjan V. Shentov (Reg. No. 38051), and Kenneth L. Stein (Reg. No. 38704), all of Pennie & Edmonds LLP, whose addresses are 1155 Avenue of the Americas, New York, New York 10036, 1667 K Street N.W., Washington, DC 20006 and 3300 Hillview Avenue, Palo Alto, CA 94304, and each of them, my attorneys, to prosecute this application, and to transact all business in the Patent and Trademark Office connected therewith.

## SEND CORRESPONDENCE TO:

PENNIE & EDMONDS LLP  
1155 Avenue of the Americas  
New York, N.Y. 10036-2711  
PTO Customer No. 20583

DIRECT TELEPHONE CALLS TO:  
PENNIE & EDMONDS LLP DOCKETING  
(212) 790-2803

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2 0 1	FULL NAME OF INVENTOR	LAST NAME Cerami	FIRST NAME Anthony	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY Sleepy Hollow	STATE OR FOREIGN COUNTRY New York	COUNTRY OF CITIZENSHIP United States
	POST OFFICE ADDRESS	STREET 121 Farrington Avenue	CITY Sleepy Hollow	STATE OR COUNTRY New York
	SIGNATURE OF INVENTOR 201			DATE
2 0 2	FULL NAME OF INVENTOR	LAST NAME Cerami	FIRST NAME Carla	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY Sleepy Hollow	STATE OR FOREIGN COUNTRY New York	COUNTRY OF CITIZENSHIP United States
	POST OFFICE ADDRESS	STREET 121 Farrington Avenue	CITY Sleepy Hollow	STATE OR COUNTRY New York
	SIGNATURE OF INVENTOR 202			DATE
2 0 3	FULL NAME OF INVENTOR	LAST NAME Xie	FIRST NAME Qiao-wen	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY Yonkers	STATE OR FOREIGN COUNTRY New York	COUNTRY OF CITIZENSHIP United States
	POST OFFICE ADDRESS	STREET 30 Sidehill Lane	CITY Yonkers	STATE OR COUNTRY New York
	SIGNATURE OF INVENTOR 203			DATE
2 0 4	FULL NAME OF INVENTOR	LAST NAME TenHuisen	FIRST NAME Kevor	MIDDLE NAME S.
	RESIDENCE & CITIZENSHIP	CITY Clinton	STATE OR FOREIGN COUNTRY New Jersey	COUNTRY OF CITIZENSHIP United States
	POST OFFICE ADDRESS	STREET 40 Alexandra Way	CITY Clinton	STATE OR COUNTRY New Jersey
	SIGNATURE OF INVENTOR 204			DATE
2 0 5	FULL NAME OF INVENTOR	LAST NAME Rosenblatt	FIRST NAME Joel	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY Watchung	STATE OR FOREIGN COUNTRY New Jersey	COUNTRY OF CITIZENSHIP United States
	POST OFFICE ADDRESS	STREET 47 Robin Glen Road	CITY Watchung	STATE OR COUNTRY New Jersey
	SIGNATURE OF INVENTOR 205			DATE

2 0 6	FULL NAME OF INVENTOR	LAST NAME Koyfman	FIRST NAME Ilya	MIDDLE NAME S.	
	RESIDENCE & CITIZENSHIP	CITY Ringoess	STATE OR FOREIGN COUNTRY New Jersey	COUNTRY OF CITIZENSHIP United States	
	POST OFFICE ADDRESS	STREET 5 Messenger Lane	CITY New Jersey	STATE OR COUNTRY New Jersey	ZIP CODE 08551
		SIGNATURE OF INVENTOR 206			DATE

## **EXHIBIT C**

NEW YORK  
1155 AVENUE OF THE AMERICAS  
NEW YORK, NY 10036-2711  
(212) 790-9090  
FACSIMILE: (212) 869-8864/9741

WASHINGTON, D.C.  
1667 K STREET, N.W.  
WASHINGTON, D.C. 20006-1605  
(202) 496-4400  
FACSIMILE: (202) 496-4444

PALO ALTO  
3300 HILLVIEW AVENUE  
PALO ALTO, CALIFORNIA 94304-1203  
(650) 493-4935  
FACSIMILE (650) 493-5556

May 28, 2002

***Via Certified Mail – Return Receipt Requested***

Our Ref. No.: 10162-0006-999

WRITER'S DIRECT DIAL:  
(212) 790-6447  
INTERNET ADDRESS:  
[RYANM@PENNIE.COM](mailto:RYANM@PENNIE.COM)

Mr. Joel Rosenblatt  
47 Robin Glen Road  
Watchung, New Jersey 07060

Re: U.S. Patent Application Serial No. 10/017,457  
Filed: December 7, 2001  
For: IMMUNE MODULATION DEVICE FOR USE IN ANIMALS  
By: A. Cerami, C. Cerami, Q. Xie, K. TenHuisen, J. Rosenblatt and I. Koyfman

Dear Mr. Rosenblatt:

Enclosed for your records is a copy of the Filing Receipt and a copy of the License for Foreign Filing that were mailed March 21, 2002, from the U.S. Patent and Trademark Office in connection with the above-identified nonprovisional patent application. The Filing Receipt confirms the filing date and serial number for the above-captioned patent application.

Also enclosed is a copy of a Notice to File Missing Parts of Nonprovisional Application. This Notice indicates that an executed Declaration must be filed.

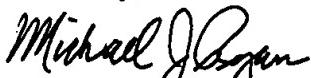
Accordingly, please review the enclosed copy of the above-identified patent application, as filed, and then sign and date the enclosed Declaration and Power of Attorney. Once you have done so, please return the executed Declaration and Power of Attorney to us for filing with the U.S. Patent and Trademark Office in response to the Notice to File Missing Parts.

Since the above identified-application will claim priority to the U.S. non-provisional patent application filed on May 11, 2001, which is directed to the same invention, we would appreciate it if you would provide us with a copy of the filling receipt or at least the application serial number for the provisional application.

Mr. Joel Rosenblatt  
May 28, 2002  
Page 2

Thank you for your assistance in this matter. Should you have any questions regarding the above, please do not hesitate to contact us.

Sincerely,

  
Michael J. Ryan

Enclosures

cc: Mr. Kevor S. TenHuisen (w/encs)  
Ms. Ilya S. Koyfman (w/encs)  
Anthony Cerami, Ph.D.  
Carla Cerami, M.D., Ph.D.  
Qiao-wen Xie, Ph.D.  
Hal Brent Woodrow, Esq. (w/o encs)  
Laura A. Coruzzi, Esq.



Mr. Joel Rosenblatt  
May 28, 2002  
Page 3

bc: Ann L. Gisolfi, Esq.

**SENDER: COMPLETE THIS SECTION**

- Complete Items 1, 2, and 3. Also complete item 4 if Restricted Delivery is desired.
- Print your name and address on the reverse so that we can return the card to you.
- Attach this card to the back of the mailpiece, or on the front if space permits.

1. Article Addressed to:

**Mr. Joel Rosenblatt**  
**47 Robin Glen Road**  
**Watchung, NJ 07060**

**COMPLETE THIS SECTION ON DELIVERY**

A. Signature

**X**
 Agent  
 Addressee

B. Received by (Printed Name)

C. Date of Delivery

D. Is delivery address different from item 1?  YesIf YES, enter delivery address below:  No

3. Service Type

Certified Mail     Express Mail  
 Registered     Return Receipt for Merchandise  
 Insured Mail     C.O.D.

4. Restricted Delivery? (Extra Fee)  Yes

2. Article Number

(Transfer from service label)

7099 3400 0017 1340 3089

PS Form 3811, August 2001

Domestic Return Receipt

102595-01-M-2509



7099 3400 0017 1340 3089  
 7099 3400 0017 1340 3089  
 7099 3400 0017 1340 3089  
 7099 3400 0017 1340 3089

**U.S. Postal Service**  
**CERTIFIED MAIL RECEIPT**  
*(Domestic Mail Only; No Insurance Coverage Provided)*

10162-006 MJR/NMoore

Postage	\$	Postmark Here
Certified Fee		
Return Receipt Fee (Endorsement Required)		
Restricted Delivery Fee (Endorsement Required)		
<b>Total Postage &amp; Fees</b> \$		

Recipient's Name (Please Print Clearly) (to be completed by maller)  
**Mr. Joel Rosenblatt**

Street, Apt. No., or P.O. Box No.

**47 Robin Glen Road**

City, State, ZIP+4

**Watchung, NJ 07060**

PS Form 3800, February 2000

See Reverse for Instructions

## DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below at 201 et seq. underneath my name.

I believe I am the original, first and sole inventor if only one name is listed at 201 below, or an original, first and joint inventor if plural names are listed at 201 et seq. below, of the subject matter which is claimed and for which a patent is sought on the invention entitled

## IMMUNE MODULATION DEVICE FOR USE IN ANIMALS

and for which a patent application:

- is attached hereto and includes amendment(s) filed on *(if applicable)*  
 was filed in the United States on December 7, 2001 as Application No. 10/017,457 *(for declaration not accompanying application)*  
 with amendment(s) filed on *(if applicable)*  
 was filed as PCT international Application No. on and was amended under PCT Article 19 on *(if applicable)*

I hereby state that I have reviewed and understand the contents of the above identified application, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED PRIOR TO THE FILING DATE OF THE APPLICATION			
APPLICATION NUMBER	COUNTRY	DATE OF FILING (day, month, year)	PRIORITY CLAIMED
			YES <input type="checkbox"/> NO <input type="checkbox"/>
			YES <input type="checkbox"/> NO <input type="checkbox"/>

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below.

APPLICATION NUMBER	FILING DATE
60/****, ***	May 11, 2001

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

APPLICATION SERIAL NO.	FILING DATE	STATUS		
		PATENTED	PENDING	ABANDONED

POWER OF ATTORNEY: As a named inventor, I hereby appoint Berj A. Terzian (Reg. No. 20060), David Weild, III (Reg. No. 21094), Barry D. Rein (Reg. No. 22411), Stanton T. Lawrence, III (Reg. No. 25736), Charles E. McKenney (Reg. No. 22795), Philip T. Shannon (Reg. No. 24278), Francis E. Morris (Reg. No. 24615), Charles E. Miller (Reg. No. 24576), Gidon D. Stern (Reg. No. 27469), John J. Lauter, Jr. (Reg. No. 27814), Brian M. Poissant (Reg. No. 28462), Brian D. Coggio (Reg. No. 27624), Rory J. Radding (Reg. No. 28749), Stephen J. Harbulak (Reg. No. 29166), Donald J. Goodell (Reg. No. 19766), Thomas E. Friebel (Reg. No. 29258), Laura A. Coruzzi (Reg. No. 30742), Jennifer Gordon (Reg. No. 30753), Geraldine F. Baldwin (Reg. No. 31232), Victor N. Balancia (Reg. No. 31231), Samuel B. Abrams (Reg. No. 30605), Steven I. Wallach (Reg. No. 35402), Marcia H. Sundeen (Reg. No. 30893), Paul J. Zegger (Reg. No. 33821), Edmond R. Bannon (Reg. No. 32110), Bruce J. Barker (Reg. No. 33291), Adriane M. Antler (Reg. No. 32605), Thomas G. Rowan (Reg. No. 34419), James G. Markey (Reg. No. 31636), Thomas D. Kohler (Reg. No. 32797), Scott D. Stimpson (Reg. No. 33607), Gary S. Williams (Reg. No. 31066), Ann L. Gisolfi (Reg. No. 31956), Todd A. Wagner (Reg. No. 35399), Scott B. Familiant (Reg. No. 35514), Kelly D. Talcott (Reg. No. 39582), Francis D. Cerrito (Reg. No. 38100), Anthony M. Insogna (Reg. No. 35203), Brian M. Rothery (Reg. No. 35340), Brian D. Siff (Reg. No. 35679), Michael J. Lyons (Reg. No. 37386), Garland T. Stephens (Reg. No. 37242), William J. Sipio (Reg. No. 34514), Nikolaos C. George (Reg. No. 39201), Stephen S. Rabinowitz (Reg. No. 40286), Ognjan V. Shentov (Reg. No. 38051), and Kenneth L. Stein (Reg. No. 38704), all of Pennie & Edmonds LLP, whose addresses are 1155 Avenue of the Americas, New York, New York 10036, 1667 K Street N.W., Washington, DC 20006 and 3300 Hillview Avenue, Palo Alto, CA 94304, and each of them, my attorneys, to prosecute this application, and to transact all business in the Patent and Trademark Office connected therewith.

## SEND CORRESPONDENCE TO:

PENNIE & EDMONDS LLP  
1155 Avenue of the Americas  
New York, N.Y. 10036-2711  
PTO Customer No. 20583

DIRECT TELEPHONE CALLS TO:  
PENNIE & EDMONDS LLP DOCKETING  
(212) 790-2803

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

2 0 1	FULL NAME OF INVENTOR	LAST NAME Cerami	FIRST NAME Anthony	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY Sleepy Hollow	STATE OR FOREIGN COUNTRY New York	COUNTRY OF CITIZENSHIP United States
	POST OFFICE ADDRESS	STREET 121 Farrington Avenue	CITY Sleepy Hollow	STATE OR COUNTRY New York
	SIGNATURE OF INVENTOR 201		DATE	
2 0 2	FULL NAME OF INVENTOR	LAST NAME Cerami	FIRST NAME Carla	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY Sleepy Hollow	STATE OR FOREIGN COUNTRY New York	COUNTRY OF CITIZENSHIP United States
	POST OFFICE ADDRESS	STREET 121 Farrington Avenue	CITY Sleepy Hollow	STATE OR COUNTRY New York
	SIGNATURE OF INVENTOR 202		DATE	
2 0 3	FULL NAME OF INVENTOR	LAST NAME Xie	FIRST NAME Qiao-wen	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY Yonkers	STATE OR FOREIGN COUNTRY New York	COUNTRY OF CITIZENSHIP United States
	POST OFFICE ADDRESS	STREET 30 Sidehill Lane	CITY Yonkers	STATE OR COUNTRY New York
	SIGNATURE OF INVENTOR 203		DATE	
2 0 4	FULL NAME OF INVENTOR	LAST NAME TenHuisen	FIRST NAME Kevor	MIDDLE NAME S.
	RESIDENCE & CITIZENSHIP	CITY Clinton	STATE OR FOREIGN COUNTRY New Jersey	COUNTRY OF CITIZENSHIP United States
	POST OFFICE ADDRESS	STREET 40 Alexandra Way	CITY Clinton	STATE OR COUNTRY New Jersey
	SIGNATURE OF INVENTOR 204		DATE	
2 0 5	FULL NAME OF INVENTOR	LAST NAME Rosenblatt	FIRST NAME Joel	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY Watchung	STATE OR FOREIGN COUNTRY New Jersey	COUNTRY OF CITIZENSHIP United States
	POST OFFICE ADDRESS	STREET 47 Robin Glen Road	CITY Watchung	STATE OR COUNTRY New Jersey
	SIGNATURE OF INVENTOR 205		DATE	

2 0 6	FULL NAME OF INVENTOR	LAST NAME Koyfman	FIRST NAME Ilya	MIDDLE NAME S.	
	RESIDENCE & CITIZENSHIP	CITY Ringoess	STATE OR FOREIGN COUNTRY New Jersey	COUNTRY OF CITIZENSHIP United States	
	POST OFFICE ADDRESS	STREET 5 Messenger Lane	CITY New Jersey	STATE OR COUNTRY New Jersey	ZIP CODE 08551
		SIGNATURE OF INVENTOR 206		DATE	

## **EXHIBIT D**

**SENDER: COMPLETE THIS SECTION**

- Complete items 1, 2, and 3. Also complete item 4 if Restricted Delivery is desired.
- Print your name and address on the reverse so that we can return the card to you.
- Attach this card to the back of the mailpiece, or on the front if space permits.

## 1. Article Addressed to:

**Ms. Ilya S. Koyfman**  
**5 Messenger Lange**  
**Ringoes, NJ 08551**

**COMPLETE THIS SECTION ON DELIVERY**

## A. Signature

**X Y. Polasey**

Agent  
 Addressee

## B. Received by (Printed Name)

## C. Date of Delivery

**Aug 5/3/00**

D. Is delivery address different from item 1?  Yes  
 If YES, enter delivery address below:  No

## 3. Service Type

- |  |  |
|--|--|
| <input checked="" type="checkbox"/> Certified Mail | <input type="checkbox"/> Express Mail                              |
| <input type="checkbox"/> Registered                | <input checked="" type="checkbox"/> Return Receipt for Merchandise |
| <input type="checkbox"/> Insured Mail              | <input type="checkbox"/> C.O.D.                                    |

4. Restricted Delivery? (Extra Fee)  Yes

## 2. Article Number

(*Enter from service label*) **7099 3400 0017 1340 3072**

PS Form 3811, August 2001

Domestic Return Receipt

102595-01-M-2509

**SENDER: COMPLETE THIS SECTION**

- Complete items 1, 2, and 3. Also complete item 4 if Restricted Delivery is desired.
- Print your name and address on the reverse so that we can return the card to you.
- Attach this card to the back of the mailpiece, or on the front if space permits.

## 1. Article Addressed to:

**Mr. Joel Rosenblatt**  
**47 Robin Glen Road**  
**Watchung, NJ 07060**

**COMPLETE THIS SECTION ON DELIVERY**

## A. Signature

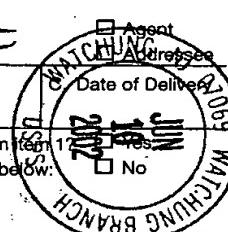
**X Joel Rosenblatt**

Agent  
 Addressee

## C. Date of Delivery

**Aug 5/3/00**

D. Is delivery address different from item 1?  Yes  
 If YES, enter delivery address below:  No



## 3. Service Type

- |  |  |
|--|--|
| <input checked="" type="checkbox"/> Certified Mail | <input type="checkbox"/> Express Mail                              |
| <input type="checkbox"/> Registered                | <input checked="" type="checkbox"/> Return Receipt for Merchandise |
| <input type="checkbox"/> Insured Mail              | <input type="checkbox"/> C.O.D.                                    |

4. Restricted Delivery? (Extra Fee)  Yes

## 2. Article Number

(*Enter from service label*) **7099 3400 0017 1340 3089**

PS Form 3811, August 2001

Domestic Return Receipt

102595-01-M-2509

**SENDER: COMPLETE THIS SECTION**

- Complete items 1, 2, and 3. Also complete item 4 if Restricted Delivery is desired.
- Print your name and address on the reverse so that we can return the card to you.
- Attach this card to the back of the mailpiece, or on the front if space permits.

## 1. Article Addressed to:

**Mr. Kevor S. TenHuisen**  
**40 Alexandra Way**  
**Clinton, NJ 08809**

**COMPLETE THIS SECTION ON DELIVERY**

## A. Signature

**X Kevor S. TenHuisen**

Agent  
 Addressee

## C. Date of Delivery

**Aug 5/3/00**

D. Is delivery address different from item 1?  Yes  
 If YES, enter delivery address below:  No



## 3. Service Type

- |  |  |
|--|--|
| <input checked="" type="checkbox"/> Certified Mail | <input type="checkbox"/> Express Mail                              |
| <input type="checkbox"/> Registered                | <input checked="" type="checkbox"/> Return Receipt for Merchandise |
| <input type="checkbox"/> Insured Mail              | <input type="checkbox"/> C.O.D.                                    |

4. Restricted Delivery? (Extra Fee)  Yes

## 2. Article Number

(*Enter from service label*) **7099 3400 0017 1340 3096**

PS Form 3811, August 2001

Domestic Return Receipt

102595-01-M-2509

## **EXHIBIT E**

# *Johnson & Johnson*

OFFICE OF  
GENERAL COUNSEL

ONE JOHNSON & JOHNSON PLAZA  
NEW BRUNSWICK, N.J. 08933-7003

June 19, 2002

Michael J. Ryan, Esquire  
**Pennie & Edmonds, LLP**  
1155 Avenue of The Americas  
New York, NY 10036

**Re: U.S. Patent Application Serial No. 10/017,457**  
**Immune Modulation Device for Use in Animals**  
**Our Docket No.: ORT1295**

Dear Mr. Ryan:

I am in receipt of your letter to Messieurs TenHuisen, Rosenblatt and Koyfman dated May 28, 2002. Included therein were a copy of United States Patent Application Serial No. 10/017,457, filed by yourself and Ms. Coruzzi, and Declaration and Power of Attorney regarding the application prepared by your firm for execution by each individual.

Initially, as you most certainly must be aware, all of the above individuals are employees of Ethicon, Inc. and are duly represented by counsel. Contact of these individuals by your firm is improper and we must insist that you refrain from making any further contact with any Ethicon employees.

In addition, no representative of Pennie and Edmonds has the authority to represent either the individuals or Johnson & Johnson affiliates in this matter. The Declarations and Power of Attorney will not be executed.

As both the Cerami's and Ms. Coruzzi are aware, prior to filing our application to which US 10/017,457 claims priority, and which is substantially identical to US 10/017,457, Mr. Woodrow gave the Cerami's and Ms. Xie ample opportunity to provide corroborated evidence of their claim to inventorship with respect to claims filed in our application. The Cerami's and Ms. Xie simply refused or were unable to allege any facts or provide any evidence to support any such claim. Our records do not reflect any information that

Michael J. Ryan, Esquire

2.

June 19, 2002

would support the claim to inventorship by the Cerami's or Ms. Xie. To date, we still have no reason to believe that either the Cerami's or Ms. Xie are rightful inventors to any claims of US 10/017,457 or our application to which it claims priority. Consequently, we believe that the inventorship you have listed in US 10/017,457 is inaccurate and the claim to priority improper.

Any future correspondence regarding this matter should be directed to my attention.

Very truly yours,

Johnson & Johnson



Kent Wissing

WKKW/c

CC:      M. S. Goodwin  
          I. S. Koyfman  
          J. Rosenblatt  
          K. TenHuisen  
          H. B. Woodrow